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PERFORATED PEPTIC ULCER*

A Follow-Up Study of One Hundred Cases

ASHBEL C. WILLIAMS, M.D.†

BOSTON

DOES operative closure of an acutely perforated ulcer result in cure of the ulcer? Is acute perforation of a peptic ulcer an indication for gastric resection? What is the prognosis, and what regime should be recommended after a patient has recovered from the immediate episode of an acute perforation? In which cases is further surgery indicated?

The ensuing study was undertaken for the purpose of gathering information that would be helpful in answering such questions as the above and that, from a broader standpoint, would contribute to the establishment of sound criteria governing the follow-up management of perforated peptic ulcer. A number of papers dealing with perforated peptic ulcer have appeared in the literature during the past twenty years, but these publications have been concerned for the most part with the diagnosis and operative treatment of the acute perforation. In the present study, these latter aspects will be only briefly mentioned, emphasis being placed on the follow-up results and ultimate prognosis.

No attempt will be made to review the literature, since a fairly complete review was published by Sallick[1] in 1936.

MATERIAL

From the record files of the Boston City Hospital a complete roster was obtained of all the patients operated on for acutely perforated peptic ulcer at that institution from 1934 to 1941, inclusive. Those patients who died during the period of postoperative hospitalization were excluded, leaving about 300 patients who survived the immediate convalescence. These patients were requested by letter to return to the Outpatient Department for follow-up studies, and 104 of them complied. For simplicity of statistics the last four patients responding were not included in this study. They did not differ significantly from the preceding 100 patients, every one of whom was interviewed and examined by me on one or more occasions, a gastrointestinal barium study being requested in each case. Patients who replied by letter or telephone and did not report in person were also excluded. Previous to this study, the majority of the patients had returned to the Outpatient Department on several occasions for follow-up examinations or treatment. Their previous outpatient records and the inpatient records in all cases were carefully studied. Every effort was directed toward making observations both impartial and accurate.

In the present series, 27 of the patients were in the fourth and 32 in the fifth decade at the time of perforation. The incidence falls steadily as one proceeds toward the younger and older age groups. The youngest patient was nineteen years of age and the oldest seventy-four. Ninety-seven patients were males and 3 per cent were females. This unexplained preponderance of perforation in the male sex has been noted in all previous studies.

The average length of the follow-up period was three years and four months, the longest period being twelve years and the shortest six months.

The ulcer was gastric in 54 cases, — prepyloric in 42 and located elsewhere in the stomach in 12, — duodenal in 40, and pyloric in 3; in the remaining 3 cases the exact site was not stated. In all cases the ulcers were in the anterior wall of the stomach or bowel. There were no cases of multiple perforations occurring simultaneously.

SURGERY OF THE ACUTE PERFORATION

The operative treatment of the acute perforation has been the source of considerable diversity of opinion. A review of the recent literature reveals, however, that a substantial majority of surgeons regard simple suture as the procedure of choice.[1-6] Gastroenterostomy is thought to be indicated in addition to simple suture only in cases in which the pylorus is so encroached on as to make complete obstruction a probable complication. There is

*From the Third Surgical Service, Boston City Hospital, and the Boston University School of Medicine.

†Formerly surgical resident, Boston City Hospital, and assistant in surgery, Boston University School of Medicine.

little justification for other procedures. It seems wisest to perform the simplest operation that will tide the patient over the emergency.

Simple suture alone was employed in 94 cases in this series. Local excision of the ulcer followed by suture of the resulting defect was performed in 2 cases. In 2 cases gastroenterostomy was performed along with simple closure of the ulcer. The ulcer was excised and pyloroplasty carried out in 1 case. Appendectomy was performed in addition to simple suture in 1 case, the original diagnosis having been acute appendicitis. It thus becomes obvious that this study is concerned almost entirely with the follow-up of patients treated by simple suture alone. The other procedures were too few to be of any statistical significance.

No effort was made to determine the operative mortality of the acute perforation among the 300-odd patients treated during the period from 1934 through 1941. However, Morrison,[7] also working at the Boston City Hospital, in a statistical analysis of 200 cases of acutely perforated ulcer found the operative mortality to be 21 per cent. Although his study was carried out from 1930 through 1935, his figures apply in a general manner to the series of cases considered herein.

Following suture of the perforation, the average patient at the Boston City Hospital was maintained on parenteral fluids for one to four days and then started on frequent feedings of water, milk and cream, and Sippy powders. A week or ten days postoperatively a progressive convalescent Sippy diet was allowed. When discharged the patient was given printed instructions outlining an ulcer regime based chiefly on a full Sippy diet, the use of alkalis and tincture of belladonna and abstinence from alcohol and tobacco. The present paper is chiefly concerned with what happens to the patient from this stage on; that is, commencing with his discharge from the hospital.

Follow-up Results

It is perhaps best to begin with a presentation of figures regarding the follow-up results in this study. These results were appraised as excellent in 28 cases, as good in 27, as fair in 22 and as poor in 23. Results were considered as excellent when there was no recurrence of symptoms, barium studies showed no ulcer activity and the patient was able to return to and remain at work. They were classed as good when mild symptoms such as occasional epigastric discomfort and belching of gas were experienced but did not interfere with work and were easily controlled by diet. They were described as fair when the patient experienced fairly frequent recurrences of synptoms and when there was occasional loss of time from work or the x-ray showed some evidence of ulcer activity such as marked spasm or an ulcer crater. The results were considered poor when the symptoms were so constant and severe as to make attendance at work irregular or impossible or in which repeated hospitalizations were necessitated. In this category also fall the cases in which obstruction developed, second perforations occurred or further surgical procedures were performed for the relief of symptoms.

By pooling the excellent and good results on the one hand and the fair and poor results on the other, all the cases may be roughly grouped as satisfactory or unsatisfactory, there being 55 per cent in the former group and 45 per cent in the latter.

"The life history of ulcer can be said to end only with the life of the patient."[8] Accordingly, it is obvious that the above classification of results does not represent a final analysis, since the average follow-up period was only three years and four months. It is significant, however, that of the patients who fell into the poor or fair categories, the vast majority had experienced recurrences of one sort or another within six months after perforation. In other words, what happens to a patient during the first six months to one year after perforation is a relatively accurate guide to his future course. Few patients who were symptom free for as long as a year had any serious recurrences at a later date.

Duration of Symptoms Prior to Perforation As a Guide to Prognosis

It is a well-known fact that acute perforations often occur in persons who have never suffered from ulcer symptoms of any sort. There were 23 such cases in this group. Following perforation, 17 of these enjoyed a satisfactory result, and the remaining experienced difficulties such as to class them as having unsatisfactory results. There were 14 patients who had experienced symptoms for less than six months prior to perforation; 8 of these had satisfactory and 6 unsatisfactory results. In 57 cases symptoms had existed for from six months to many years prior to perforation; of this group, 25 patients experienced satisfactory and 32 unsatisfactory results. In summary, the longer the pre-perforation symptoms the poorer the postperforation results. Thus the presence or absence of an ulcer history prior to perforation has prognostic significance. Unsatisfactory late results were over twice as frequent among patients who had had symptoms for six months or longer as among those who gave no history of pre-perforation symptoms.

There were 31 patients who gave a history of severe symptoms prior to perforation. Of these, 23 had unsatisfactory and 8 satisfactory late results. Thus, a patient who has suffered markedly from ulcer symptoms prior to perforation, regardless of the duration of such symptoms, has about one chance in four of a successful late result.

Influence of Diet, Alcohol and Tobacco on Recurrences

The relation of diet, alcohol and tobacco to post-perforation recurrence of ulcer symptoms was investigated. Surprisingly, among a group of 25 patients who had made no effort to diet the recurrence rate was 40 per cent, whereas of 44 patients who had attempted to follow a diet it was 45 per cent. These figures serve chiefly to emphasize that there are factors that may be more potent than diet in determining the behavior of an ulcer. The patients who were able to remain well without dieting undoubtedly suffered from less virulent ulcer tendencies and found by experience that dieting was unnecessary. On the other hand, the patients who followed their diets for years did so for the most part because they had symptoms either in spite of dieting or whenever the diet was neglected. In short, their ulcers were of a more stubborn and potent nature. Thus, deductions that might be made from a statistical study of the relation of diet to ulcer are of limited significance. The same may be said of alcohol and tobacco. Many patients in this group partook moderately of alcohol and even excessively of cigarettes and yet remained symptom free.

Before the reader takes issue with the preceding paragraph, I hasten to state that there was a group of patients — namely, the 23 whose follow-up results were classified as poor — in whom adherence to diet and abstinence from alcohol and tobacco were of the utmost importance. Indiscretions along these lines in such patients precipitated symptoms almost as constantly as a barometer reflects changes in the weather.

As has been seen, the necessity for following a strict ulcer regime varies from patient to patient, and in any one patient is unpredictable at the outset. It is therefore essential to assume the worst and to insist on a strict regime for every patient indefinitely or until, over a period of years, his ulcer proclivities have been thoroughly assessed. If dietary liberties are allowed and are followed by a recurrence of symptoms, one should close the door forever on such liberties for that patient. It is far wiser to explain to every patient at the outset that he must adhere to an ulcer regime for the rest of his life and that the bars can be let down only at the peril of firing anew the embers of ulcer activity. It is a distressing and frequent experience to learn from a patient in the throes of recurrence that he was told by his physician that dietary restrictions were only an expedient to aid convalescence and could be dropped after that stage.

Correlation Between X-ray Examinations and Symptoms

Barium studies were first ordered in all cases in which symptoms were severe. Then, since some patients apparently have ulcers that, although active, are relatively asymptomatic, it was decided that x-ray examination should be made in all cases. Seventy-eight of the 100 patients reported for this examination. Eight additional patients had had such an examination fairly recently, so that barium studies were available in 86 of the 100 cases.

X-ray films were considered positive for ulcer, either active or chronic, under the following circumstances: when an ulcer crater was visualized; when there was pyloric obstruction with a gastric residue; and when persistent marked tenderness and spasm of the duodenal cap were noted in repeated studies.

Measured by the above criteria, x-ray examination showed ulcer activity in 50 (58 per cent) of the 86 patients who were subjected to such studies. Of these 50, symptoms varying from moderate to severe were present in 40 cases (80 per cent), and no symptoms whatsoever had been suffered in 10 (20 per cent). Barium studies were negative for ulcer activity in 36 cases (42 per cent). Twenty (55 per cent) of these patients were asymptomatic and 16 (45 per cent) had suffered from symptoms, which were mild in 12 cases and severe in 4.

It may be seen from the above that the x-ray findings were in complete agreement with the symptomatology in 69 per cent of the cases examined; there was only a slight divergence between these two factors in another 14 per cent, and there was no correlation whatsoever between the symptoms and the x-ray findings in 16 per cent. These latter discrepancies may be explained partly on the basis of inaccuracies in x-ray diagnosis on the one hand and the unquestionable existence of silent ulcers on the other. Deformities resulting from the surgical treatment of the acute perforation are difficult to evaluate and to differentiate from ulcer. Also, the significance of spasm and tenderness is always open to question. In short, it is important to realize that x-ray and fluoroscopy have limitations and that decisions should never be made through these mediums alone.

Second Perforations

Three patients experienced a second acute perforation. One of these patients was sixty-seven years of age. He had suffered from symptoms prior to his first perforation but said that his second came "out of a clear sky" ten months later. He has not followed a strict diet since this last perforation, drinks beer freely, has an active duodenal ulcer as shown by x-ray examination and has recurrent symptoms. Surgery was advised but refused. This patient will undoubtedly experience further trouble.

Another of these patients was seventy-four years of age. He had had symptoms for twenty years prior to his first perforation. The second perforation came eight years later, the interval being marked by transient moderate symptoms. He has had

severe recurrent symptoms, and recent x-ray examination showed an active prepyloric ulcer. This patient improved after strict dieting. Surgery was withheld because of his age and because he presented a poor surgical risk.

The third patient was forty-six years of age. He had experienced symptoms for only fifteen hours prior to his first perforation, which was duodenal. Four years later he experienced a second perforation, also duodenal. The interval was marked by symptoms and failure to follow a diet. A recent barium study showed a penetrating duodenal ulcer. This patient is awaiting gastric resection, which has been advised.

These experiences, although brief, are typical of others reported in the literature.

For several reasons it is concluded that a second perforation should be considered an indication for elective subtotal gastric resection. First, an ulcer that perforates twice is of a virulent, persistent nature and is likely to lead to further grave complications. Second, these patients have not adhered strictly to an ulcer regime in most cases, even though vividly aware of the consequences of laxity in this regard. If a patient does not conform to restrictions after he has experienced one perforation, there is little cause to assume that he will ever do so. Of course, if following an acute perforation a patient is told that an ulcer regime is unnecessary or is told nothing and fails to adhere to a regime through ignorance of it, he cannot be held at fault if a second perforation occurs. He is still entitled to a trial of medical treatment, and not unless he has recurrence under such treatment should he be subjected to surgery.

Carcinoma in a Gastric Ulcer

Carcinoma apparently developed in a gastric ulcer in one of the cases of this series. The patient was fifty years of age. At the time of perforation the lesion was prepyloric and on the lesser curvature. Carcinoma was suspected because of widespread induration, but biopsy showed only chronic inflammation. X-ray films were negative one year after perforation and the patient was free of symptoms for two years, but then began to lose weight and to experience severe epigastric pain and vomiting. The x-ray diagnosis was prepyloric carcinoma. A subtotal gastric resection was performed and an easily resectable colloid carcinoma of moderate size was found in the exact site of the previous ulcer. This patient has remained free of symptoms for four months.

The possibility of the development of carcinoma is certainly to be kept in mind and is an added reason for leaning toward subtotal resection for chronic gastric ulcers, especially in cases in which ulcers have perforated. Walters[9] believes strongly that surgery is indicated for chronic gastric ulcers in general.

Secondary Surgical Procedures

Secondary surgical procedures were performed in 11 patients of this series. The indications were as follows: intractability, 5 cases; pyloric stenosis, 4 cases; carcinoma, 1 case; and possible carcinoma, 1 case. Subtotal gastric resection was performed in 7 of these cases. There was no operative mortality, and all these patients have remained symptom free for one to six months. Posterior gastroenterostomy was performed in 3 cases. These patients have remained well for nineteen to seventy-two months.

Partial gastric resection, excluding the ulcer (duodenal) by leaving the pylorus, was performed in 1 case. The pyloric and adjacent antral mucosas were not excised. The patient died following a perforation through the suture line of the gastroenterostomy, the perforation occurring on the nineteenth postoperative day. This patient had had a high gastric acidity, had had two massive hemorrhages in addition to his perforation and had suffered from severe ulcer pains. A subtotal gastric resection including the ulcer was indicated and would probably have been curative.

There are too few cases in this group and the follow-up periods are too brief to make further discussion of the operative results worth while.

There were 12 additional patients whose ulcer symptomatology and x-ray findings were such as to call for subtotal gastric resection. Most of them refused operation. In 3 cases they were such poor risks that surgery had to be withheld.

Combining the 11 patients who had secondary surgical procedures with the 12 who should have had them, one obtains a group of 23 cases in which further surgery was indicated. In other words, in almost one fourth of the cases the follow-up results were sufficiently discouraging to make elective surgery feasible.

Comment

Gastric analyses were not routinely carried out in all these cases because of limited time and facilities. It is regretted that the total number of such analyses performed was not sufficient to permit a significant correlation between gastric acidity and the other factors considered in the follow-up study.

The importance of the psychic factor in the causation and aggravation of peptic ulcer is clearly recognized. It was suggestive in many of these cases that personality was a dominant cause of the ulcer difficulties. Since this factor, however, is too complex to lend itself to accurate evaluation it did not seem practical to include it in the study. The psychic factor is also the most inaccessible from a therapeutic standpoint, and it is probable that since this factor exercises a strong influence on gastric motility and secretion,[10] it is the one chiefly at fault in the ulcers that are the most stubborn and virulent in the face of medical treatment.

There seems to be a tendency among physicians and surgeons to cling to dietary efforts through an unwarranted siege of ulcer recurrences. If a patient, following a perforation, has had his condition explained to him and a regime, including diet, outlined and has still had two or more recurrences of serious symptoms in spite of his efforts to follow instructions, the physician should face the facts. He should remember that an ulcer regime has decided limitations, even when followed to the letter. Human nature greatly widens these limitations. If a patient has failed to adhere to a regime several times, there is little justification for supposing that he will do so in the future. The average patient adheres to instructions only so long as he has symptoms. Rather than theorize as to what would happen should the patient adhere strictly to instructions, one should consider what has already happened and make a decision based on facts rather than on theory. Were this done oftener, many more of these patients would come to surgery earlier in their ulcer careers and be spared no end of physical, social and financial suffering. Chronic alcoholic patients and those who are totally uncooperative from a medical standpoint should not be subjected to elective surgery, for surgery is no cure-all. Unless a patient is reasonably careful he may find himself saddled with a marginal ulcer at the gastroenterostomy even though a technically good operation has been performed.[8, 11]

The 25 per cent of patients suffering from severe recurrences should be subjected to surgery. The indications for surgery in peptic ulcer have been outlined many times. They are as follows: two or more massive hemorrhages, pyloric stenosis with obstruction, intractability and possible malignancy. To these generally accepted indications it seems wise to add the following: patients experiencing acute perforation of an ulcer for the second time, those experiencing acute perforation, preceded or followed by one or more massive hemorrhages, those experiencing severe recurrent ulcer symptoms following perforation and those experiencing perforation as a climax to a protracted ulcer history. It should be stressed that acute perforation is not in itself regarded as an indication for gastric surgery, since over half the patients do satisfactorily on a conservative regime following such perforations. This is an effective answer to those who advocate gastric resection as the procedure of choice at the time of the perforation. Neither should any patient be subjected to elective gastric surgery unless he has given medical treatment a thorough trial and failed to obtain relief.

When elective surgery becomes necessary the same procedure is indicated in ulcers that have perforated as in those that have bled or become obstructive; namely, subtotal gastric resection. This is not only the procedure of choice but is the only one that consistently gives excellent results. By subtotal resection is meant the removal of two thirds to three fourths of the stomach together with the pylorus, closing the duodenal stump blindly and re-establishing the continuity of the gastrointestinal tract through some form of gastrojejunostomy. If a pyloric or duodenal ulcer is technically hazardous to remove, subtotal resection may be performed, leaving the pylorus and ulcer in situ; this is the so-called "exclusion operation." If it is employed,[12] all antral and pyloric mucosa must be thoroughly excised before closing the pyloric stump. There is one set of circumstances in which gastroenterostomy alone is an acceptable procedure; namely, in an elderly patient having a high degree of pyloric stenosis and an extremely low gastric acidity.

The operative mortality from subtotal gastric resection in the better surgical clinics varies from 2 to 10 per cent. The mortality following this operation is no greater than that following the lesser procedures such as gastroenterostomy.[12] According to Walters,[9] Wangensteen[13] and any number of others with wide experience in this field, results following adequate surgery are excellent in 90 per cent or more of the cases. These facts are not new but that they are not fully appreciated by physicians is evidenced by the number of persons suffering from chronic ulcer that are found in the average American community.

In conclusion, two admonitions should be made concerning radical gastric surgery.

First, there are too many surgeons who speak in terms of subtotal gastric resection but who perform a partial gastric resection; who, in other words, resect less than half the stomach for the cure of ulcer. The technic of gastric resection has been standardized and repeatedly published by many of the most competent gastrointestinal surgeons. If one hopes to approach the excellent results appearing in the literature, he must begin by conforming to the principles and technic that yielded these results. Meticulous attention to every detail is essential. Neglect of any one may be fatal.

In the second place, and in line with what has just been said, gastric surgery is no field for the amateur. The consequences of a technically poor operation may be infinitely more distressing than those of a chronic ulcer. The indications for gastric surgery should be considered in relation to the ability of the surgeon.

Summary

A follow-up study of 100 cases of perforated peptic ulcer is reported.

The average length of the follow-up period was three years and four months.

The incidence of perforation was maximum in the fifth decade. There were 97 males and 3 females.

The ulcers were gastric in 54 per cent of the cases, duodenal in 40 per cent, and pyloric in 3 per cent.

Simple suture was performed for the acute perforation in 94 per cent of the cases.

The follow-up results were considered excellent in 28 per cent, good in 27 per cent, fair in 22 per cent and poor in 23 per cent of the cases.

In cases in which the symptoms prior to perforation are severe or protracted, the prognosis is poor.

Diet, alcohol and tobacco in the majority of cases are not the most important factors governing recurrences; psychic disturbances and lack of cooperation on the part of the patient, however, play significant roles.

Gastrointestinal x-ray studies were in accord with the symptomatology in 67 per cent of 86 cases.

Second perforations occurred in 3 cases. Carcinoma developed in an ulcer in 1 case.

Secondary surgical procedures were performed in 11 per cent of the cases.

Suggestions are made regarding several additional indications for elective surgery in cases of peptic ulcer.

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POLIOMYELITIS ON THE ISTHMUS OF PANAMA*

CARL E. TAYLOR, M.D.

ANCON, CANAL ZONE

ENDEMIC poliomyelitis is now recognized as being world-wide in its distribution; it is also thought to be one of the oldest human diseases.[1-6] In spite of this, only a few recent studies[7,8] of the epidemiology of endemic cases have been made. The more dramatic epidemic outbreaks, which have appeared principally in the temperate zones during the last fifty years, have been studied with great profit. The knowledge of the epidemiology of poliomyelitis is still extremely incomplete, and studies in endemic areas may contribute to it.

The widespread geographical distribution of poliomyelitis indicates that all races are susceptible to the disease. The relative susceptibility of the various races is, however, difficult to determine. Harmon[5] summarized the results of studies in the United States and concluded that Negroes seem to be less susceptible to infection than are Whites, but that once infected their mortality rate is apparently higher. Lee[9] in Hawaii found high incidence rates among Caucasians and native Hawaiians but low rates among Filipinos, Chinese and Japanese. Among the Caucasians there was a fairly general distribution through all age groups, whereas among the Orientals most of the cases were in children under five years of age. In the 1934 epidemic in the Philippine Islands, Hillman[10] stated, most of the cases occurred in white adults.

No previous studies of poliomyelitis on the Isthmus of Panama have been made. The 72 cases included in this report have been treated at Gorgas Hospital (formerly Ancon Hospital) in the thirty-eight years from 1904 to 1942. During this time there have been over 530,000 hospital admissions, with an average incidence of 1 case of poliomyelitis in 7000 admissions. Most of the cases recognized in the Canal Zone and the Republic of Panama are included in this series, but because of the extreme variability of the base population it has been impossible to derive true incidence rates. Eight hospital cases were not included in the study group because they did not meet rigid diagnostic standards or because the infection had not been contracted on the Isthmus.

*From the Board of Health Laboratory, Gorgas Hospital.

Seasonal Distribution

The annual distribution of all cases is recorded in Table 1. For comparison, there is included the total number of cases reported to the Health Department of the Panama Canal.[11] The minor discrepancies can be explained either by the fact that some hospital cases were drawn from a slightly wider geographical area than the others or by the fact that some of the cases included in the Health Department records were treated in other hospitals. Local endemicity is clearly indicated by the sprinkling of cases, with an average of slightly greater than 2 cases per year. A minor epidemic pattern is apparent when the cases are carefully analyzed for spatial and temporal proximity. In seven instances there was evidence of contact between

groups of 2 to 5 cases. These contact groups are listed in Table 2.

The most significant feature of the seasonal distribution, as indicated in Table 3, is the monthly incidence curve. A distinct unimodal peak occurred during November, December and January. All but one of the minor epidemics took place near the crest of this curve.

TABLE 1. *Annual Distribution of Poliomyelitis.*

YEAR	HOSPITAL CASES	CASES REPORTED TO HEALTH DEPARTMENT
1907	1	0
1911	1	0
1912	3	1
1915	0	1
1916	2	2
1917	0	1
1918	1	2
1919	0	1
1920	4	2
1921	2	3
1922	3	2
1923	0	1
1924	5	7
1925	10	8
1926	4	4
1927	3	5
1928	6	5
1929	3	3
1930	1	1
1931	4	2
1932	2	5
1933	4	4
1934	2	2
1935	3	4
1936	1	1
1937	1	1
1939	1	1
1940	3	3
1941	2	5
1942	0	–
Totals	72	77

RACIAL

Twenty-nine cases occurred in Whites, 26 in West Indian Negroes, 12 in Panamanians, 3 in Colombians, 1 in an Ecuadorian and 1 in a Chinese.* That the incidence in Whites is truly greater than that in Negroes is demonstrated by breaking down the figures for the Canal Zone. Only a few mestizos of Panamanian origin reside in the Canal Zone, and these are customarily included in the Negro or so-called "silver" group in Canal Zone statistics. The Canal Zone School Division has reliable statistics on the number of white and negro children living in the Canal Zone from 1928 to the present. The ratio of the total groups is approximately 3 Whites to 5 Negroes. In the 40 cases of poliomyelitis occurring primarily in the Canal Zone the ratio was 5:3. This means that poliomyelitis was two and three-fourths times as common in the Whites as in the Negroes.

*The term "race" as used herein indicates a purely utilitarian breakdown of the local color groups. Whites are United States citizens and other Caucasians. West Indian Negroes include the original relatively pure Negro group imported for the construction of the Panama Canal and their children. Panamanians include the mixed Spanish, Indian and Negro natives of the Republic of Panama.

AGE

Seventy-two per cent of the patients in this series were five years of age or less, with a median age of three. The contrast in the age distribution of the racial groups is striking. Fifty-two per cent of the Whites were five years of age or under, as compared with 85 per cent of the Negroes and 83 per cent of the Panamanians. The white population of the Isthmus of Panama has had an unusually large young-adult group. This has little significance, however, because 83 per cent of the Whites were ten years of age or under and only 2 were over twenty.

TABLE 3. *Seasonal Distribution.*

MONTH	NO. OF CASES
January	10
February	5
March	5
April	3
May	3
June	2
July	3
August	5
September	6
October	8
November	12
December	10

SEX

The total group showed the usual distribution of 43 males to 29 females. In the Whites and Panamanians there were twice as many males as females. Among the West Indian Negroes, however, the incidence was equal in the two sexes.

TABLE 2. *Contact Groups.*

TIME	PLACE	CASES	AGE yr.
December, 1916	Balboa	2 white children from the same family	6 and 11
November 11 to December 11, 1920	Cristobal and Silver City	1 white and 2 negro children in neighboring localities	1–2
April 4 to May 4, 1924	Colon	1 negro and 2 white children in the same neighborhood	2–4
September 25 to October 9, 1925	Pedro Miguel	5 white children from two neighboring families	2–7
December 20, 1926 to January 2, 1927	Panama City	2 Panamanians	3 and 5
November 23, 1931, to January 23, 1932	Silver City and Colon	3 Negroes and 1 Chinese from neighboring localities	1–2
September 27 to October 11, 1933	Balboa	2 white girls (close friends)	6 and 9

Geographical

In general, the geographical distribution followed that of the population. In the Republic of Panama, Panama City and Colon each had 13 cases; in the Canal Zone, Balboa had 9 and Pedro Miguel had 6. Only 4 cases came from the interior of Panama.

Clinical Picture

As is true in most endemic areas, the diagnosis of poliomyelitis was rarely made in the absence of paralysis. The average duration of symptoms prior to hospitalization was six and a half days — five days among the Whites, six days among the Panamanians, and eight and a half days among the West Indian Negroes.

The clinical picture was typical, the following symptoms and signs being recorded: fever, 58 cases; nausea, vomiting and anorexia, 32 cases; constipation, 7 cases; diarrhea, 1 case; headache, 15 cases; drowsiness, irritability or coma, 15 cases; mild convulsions or opisthotonos, 8 cases; early positive Brudzinski's or Kernig's signs, 6 cases; and urinary difficulty, 4 cases. Spinal-fluid determinations showed the usual lymphocytosis and increase in globulin.

Only 4 patients were free from paralysis, the diagnosis being made from prodromal symptoms and muscle tenderness in a close contact of a paralytic case. The distribution of the paralyzed muscle groups is shown in Table 4. The average period of hospitalization was thirty-eight days. The residual paralyses at the end of this time are also indicated in Table 4.

Table 4. *Distribution of Paralyses.*

Location	Primary Paralyses	Residual Paralyses
Legs:		
Right	41	30
Left	43	29
Arms:		
Right	14	8
Left	11	9
Back	13	5
Abdomen	2	1
Respiration	1	
Neck	5	1
Oculomotor	4	1
Facial	2	0
Deglutition	3	0
None	4	15

There were 5 deaths, a mortality of 6.9 per cent. Four of the fatal cases were in Whites and 1 was in a Panamanian. No deaths occurred in the West Indian Negro group. The autopsy reports record the usual neuronal damage and inflammatory reaction.

Discussion

The seasonal distribution of these cases is of interest because of the distinctive climatic conditions prevailing in Panama. The latitude of Panama is about 8° north, well within the tropics. The temperature is monotonously uniform, rarely varying from the narrow range of 68 to 95°F. The incidence of poliomyelitis in most localities shows a direct correlation with warm weather, and it has been stated that in warm climates there is a tendency toward an even distribution throughout the year.[12] Lee[9] found a seasonal curve in Hawaii, with a prolonged crest extending from February to June. In Panama the variable of temperature is so nearly controlled that one must search for correlations with other factors.

Panama has only two seasons, the wet and the dry — the latter appearing in January, February and March. With the crest of the poliomyelitis curve occurring in November, December and January one cannot say that either season is particularly favorable for transmission. Instead, it may be that the transition from wet to dry weather is important just as it is thought that the transition from warm to cold weather is important in temperate zones. Most recent studies indicate that rainfall is a negligible epidemiologic factor in other localities.[1, 4, 5] The seasonal distribution of gastrointestinal diseases in Panama is not well defined. Conner and Bates[13] reported that from 1919 to 1923 most of the cases of bacillary dysentery at Gorgas Hospital occurred in October, November and December. Macumber[14] stated that in his series of 263 cases of bacillary dysentery in the eleven-year period from 1928 to 1939 there was no significant seasonal variation. A review of his data, however, reveals that the peak month was February with 53 cases and that from October to March there were 170 cases, as contrasted with 93 cases in the six months after the onset of the rainy season. These data show a suggestive correlation between the seasonal distribution of cases of poliomyelitis and bacillary dysentery admitted to Gorgas Hospital.

The racial distribution of poliomyelitis raises several interesting questions. The greater incidence in Whites is difficult to explain. Aycock's[15] autarceologic distinctions suggest intriguing possibilities, and further studies may make it possible to apply them to racial groups. It seems significant that in both Hawaii and Panama the native populations showed involvement in distinctly younger age groups than did the Whites. Reports from the United States,[16] Scandinavia[17] and Australia[18, 19] all record a distinct shift in the age incidence of poliomyelitis during the last few decades. In earlier epidemics poliomyelitis was characteristically an infantile disease, but most of the recent studies in the predominantly Caucasian large epidemic centers show definitely that older age groups are being afflicted. In Portugal, d'Oliveira[20] reported an infantile distribution. A partial explanation that may be proposed hinges on the possibility that abortive attacks or subclinical infections have caused widespread early immunization in the temperate zones in years gone by, and that this condition still prevails among the native populations of the tropics. If one accepts the enteric route of infection, it is not difficult to postulate delayed immunization among Caucasians coincident with an improvement in sanitation. The presence of this nonimmune group would be conducive to the spread of epidemics in the temperate zones. The studies with protection neutralization

tests on monkeys, although these are admittedly crude, lend credence to this hypothesis, since protective bodies have been demonstrated with great uniformity in the blood of the native populations of several tropical and subtropical countries.[21-25] It is hoped that neutralization tests of greater specificity will be developed as a result of Armstrong's[26] transmission of the virus to the cotton rat, and that this will permit a more accurate delineation of the true geographical and racial distribution of poliomyelitis.

Summary

Seventy-two cases of endemic poliomyelitis on the Isthmus of Panama have been reviewed.

The crest of the seasonal curve occurs during November, December and January — the end of the rainy season.

Poliomyelitis was two and three-fourths times as common in Whites as in Negroes.

Among the Whites 52 per cent of the patients were five years of age or under, as contrasted with 85 per cent of the West Indian Negroes and 83 per cent of the Panamanians.

There were twice as many males as females among the Whites and Panamanians, but the incidence in the two sexes was equal in the West Indian Negroes.

There were 5 deaths, a mortality of 6.9 per cent.

Most of the cases occurred in the large population centers.

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X-RAY THERAPY OF THE HEART IN A PATIENT WITH LEUKEMIA, HEART BLOCK AND HYPERTENSION*

Report of a Case

Harry Blotner, M.D.,† and Merrill C. Sosman, M.D.‡

BOSTON

THIS is the case report of a woman who was followed for years because of vascular hypertension and who later developed myelogenous leukemia and then heart block. Since leukemia is known to infiltrate the heart muscle, it was thought that possibly a leukemic infiltration or a leukemic nodule in the heart was interfering with the conduction mechanism of the heart beat and was the cause of the heart block. If this were true, it seemed that x-ray therapy applied directly to the heart might cause the block to disappear. There are no reports in the literature of heart block treated in such a manner. Because of the result obtained with x-ray therapy in this case, it appeared of interest to present its details.

*From the Medical Clinic and Roentgen Department of the Peter Bent Brigham Hospital and the Medical Service of the Beth Israel Hospital.

†Associate visiting physician, Beth Israel Hospital.

‡Clinical professor of roentgenology, Harvard Medical School, roentgenologist, Peter Bent Brigham Hospital.

Case Report

A 64-year-old widow was known to have had a blood pressure of about 200/100 for 20 years. The blood pressure had been frequently observed during this period, and on rare occasions it rose to 250/110 and dropped to 160/90.

The records of this case begin in 1925, when the patient was at the old Beth Israel Hospital, where diagnoses of hypertension and chronic myocarditis were made. The examination was negative except for obesity, a precordial systolic murmur and hypertension. A blood Wassermann test was negative. The nonprotein nitrogen was 40 mg. per 100 cc. and the fasting blood sugar 110 mg. The heart was enlarged as shown by x-ray examination, the transverse diameter being 15 cm. and that of the chest 26.5 cm.

In 1933, the patient was admitted to the Beth Israel Hospital for possible cholecystitis, possible coronary disease and hypertensive heart disease. There was a systolic murmur over the precordium. The blood pressure varied from 235/120 to 160/90 and the pulse from 70 to 80. The white-cell count ranged from 19,600 to 9200, with no abnormal cells. The hemoglobin was 80 per cent, and the red-cell count 5,750,000. The body weight was 200 pounds. Electrocardiograms showed left-axis deviation. The urine gave a ++ test for bile on several occasions. The fasting blood sugar was 78 mg. per 100 cc., and the nonprotein nitrogen 32 mg.

From 1933 to 1940, the patient suffered from indefinite abdominal pains, nervousness and many headaches. The heart was regular, with a moderate rough precordial systolic murmur. The blood pressure was usually 200/100. She took many sedatives, and a great deal of Pyramidon for the headaches. Because one of her sons, a physician, feared leukopenia and agranulocytosis resulting from the continued use of Pyramidon, a number of white-cell and differential counts were made; these were found to be normal. In April, 1940, however, the patient had gallstone colic with jaundice, and the white-cell count during this episode ranged from 13,000 to 15,000, returning to normal after the attack disappeared. The weight was 165 pounds, and the pulse 70 to 80.

On March 9, 1941, the patient was admitted to the Peter Bent Brigham Hospital because of marked cyanosis, dyspnea, precordial distress, a temperature of 102°F. and profuse sweating. On admission the pulse was 72 and the blood pressure 204/90. The weight was 141 pounds, and there was evidence of considerable weight loss. The heart was enlarged, and there was a coarse systolic murmur over the precordium. The breath sounds were harsh, and there were a few rales at the lung bases. The liver and spleen were not palpable. The white-cell count was 127,000, with 86 per cent neutrophils, 9 per cent lymphocytes and 5 per cent myelocytes. The hemoglobin was 54 per cent (Sahli) and the red-cell count 2,900,000. The nonprotein nitrogen was 41 mg. per 100 cc. Electrocardiograms (four leads) were normal except for evidence of left-axis deviation.

On the 2nd hospital day the temperature fell to normal, where it remained thereafter. Blood Wassermann and Hinton tests were negative. X-ray examination of the chest showed marked cardiac enlargement and moderate congestion of the lungs, chiefly around the hili. Films of the right shoulder and humerus showed the bones and joints to be rather thin, and the marrow cavity considerably wider and clearer than usual, which it was believed might indicate hyperplastic bone marrow.

Basal metabolism tests on eight occasions were elevated, the first rate being + 55 per cent and the subsequent ones varying from + 39 to + 25 per cent. There was little change in the metabolism after the giving of Lugol's solution. The diagnosis was myelogenous leukemia, hypertension and cardiac decompensation.

The patient was digitalized on entry and then given 0.1 gm. of digitalis daily. Lugol's solution, 10 drops three times a day, was also prescribed. X-ray therapy in the form of a spray* was given to the trunk anteriorly and posteriorly in five treatments of 25 r each — not a large dose. Following this the white-cell count dropped to 8650 by March 26; the red-cell count was 3,000,500 and the hemoglobin 88 per cent (Sahli). The patient was discharged improved on April 11 with a white-cell count of 8650 and a weight of 135 pounds. She was instructed to take 0.05 gm. of digitalis daily and 10 drops of Lugol's solution daily, as well as iron.

After this treatment the patient continued to improve, gained weight and was fairly active. The medication was taken as prescribed. The pulse remained at 72, and the blood pressure at 210/100. On September 6, the basal metabolic rate was + 14 per cent, the pulse 72, and the weight 155 pounds. The white-cell count was 10,600, the hemoglobin 70 per cent, and the red-cell count 4,310,000. On October 21, however, when the white-cell count was 14,500, the patient began to feel tired. The white-cell count subsequently increased slowly, reaching 31,900 by March 1, 1942. X-ray therapy was again given on March 4 and 5 in the form of a spray to the trunk anteriorly and posteriorly in two treatments of 25 r each, and in 9 days the white-cell count dropped again to 9000 and the patient felt much better.

In April the patient again commenced to feel tired, weak and conscious of her heart beat and began to have a slow pulse (36 to 48), which persisted until August, the blood pressure remaining at about 210/100. The digitalis was omitted shortly after the pulse slowed, but in spite of this, the low rate persisted even though there was no coronary pain or decompensation. On July 8, when the white-cell count was 19,600, electrocardiograms showed a 2:1 heart block and left-axis deviation.

At that time it was thought that in the presence of leukemia, a leukemic nodule or infiltration involving the bundle of His might be the cause of the heart block and that x-ray therapy to the heart might cause the nodule to decrease in size and the block to disappear. It was believed that if x-ray therapy of the heart had an effect, this would begin after four or five days of treatment, because following such a period of x-ray therapy in leukemia the white-cell count usually falls appreciably. Consequently, it was decided to treat the patient in this way in the hospital. She was admitted to the Peter Bent Brigham Hospital on August 6 for x-ray therapy of the heart and was discharged on September 2. The pulse was 38 and the blood pressure 208/80. The weight was 165 pounds. The heart action was slow and regular. A third heart sound was audible, which may have been due to auricular contraction and had been present since the heart block appeared. In addition, a moderate rough systolic murmur was present over the precordium. Electrocardiograms again showed a 2:1 heart block and left-axis deviation. The white-cell count before x-ray therapy ranged from 22,000 to 24,500. The hemoglobin was 89 per cent (Sahli) and the red-cell count 4,490,000. The basal metabolic rate before x-ray therapy was +15 and +20 per cent. The blood urea nitrogen was 28 mg. per 100 cc.

X-ray therapy was directed to the heart on August 11, 12, 13, 17 and 25. The treatments given directly to the cardiac area were at the standard target-skin distance of 50 cm., using 200 kv., and a filter of 0.5 mm. of copper and 1.0 mm. of aluminum. With these factors the ionization rate measured in air was 65 r per minute. Daily doses of 200 r to the precordium were given, using a cone 15 cm. in diameter. The total skin dose in five treatments during 15 days was 1000 r.

On August 14, the pulse, which had been between 36 and 42, rose to 72 to 80 during auscultation and the third heart sound disappeared. The heart again went into block, however, and apparently was in a transitional state of being in and out of block. Electrocardiograms were taken of these phases during auscultation (Fig. 1). The pulse remained at about 80 much of the time and periodically dropped to 42. The murmur of the heart was of less intensity when it was unblocked than when it was blocked.

During the period of hospitalization a 7-foot film of the heart gave evidence of fairly marked cardiac enlargement. Fluoroscopy showed a slow beat of large amplitude with systolic expansion of the right pulmonary artery. The right auricular beat appeared in approximately 2:1 rhythm when the patient was in heart block. In the mitral annulus fibrosus there was an area of calcification that moved with the auricular beat and not with the ventricular pulsation. The heart had a transverse diameter of 17.8 cm. and the chest an internal diameter of 29.5 cm. Re-examination of the heart by x-ray when it was not in block showed its size and shape to be almost identical with those noted 11 days previously when the heart was in block.

*Spray treatment to the entire trunk, alternating front and back, is given daily in doses of 25 to 50 r a day to patients with leukemia, and has been found to be more efficient and better tolerated than concentrated treatments to the spleen or long bones with larger doses. The factors used are 200 kv., a filter of 0.5 mm. of copper and 1.0 mm. of aluminum, and a target-skin distance of 100 cm. At this distance the x-ray beam covers the entire trunk. Only the face and head are covered with lead. The ionization rate with a standard Victor chamber with these factors is 17 r per minute. This method has proved extremely effective with doses of 50 r daily in chronic leukemias. It does not cause nausea or vomiting and frequently results in prolonged regressions. In more acute cases doses of 25 r daily are used, but the results are not so good.

The patient was discharged on September 2. The pulse remained at a level of 72 for 6 days and then dropped to 42, where it remained (Fig. 2). It stayed at this level until after further x-ray treatment of the heart, beginning on November 23. Electrocardiograms repeated on several occasions when the pulse rate was slow showed a 2:1 heart block.

On November 23, the white-cell count increased to 32,500 and x-ray therapy of the heart was again given, as well as on three subsequent occasions at weekly intervals. Three days later the pulse rose to 72 for 5 minutes and then dropped to 44. X-ray therapy of the heart was repeated on December 1, 7 and 15 (Fig. 3). The white-cell count dropped to 19,800 on the last date and the pulse was 72 for several minutes. From December 17 to January 18, 1943, it ranged from 72 to 80 except for a 3-day period in December when it was 48. The blood pressure was 200/100. Subsequently the heart again went into 2:1 block, with a pulse of 48. When the white-cell count increased to 27,000 on February 4, it was decided to give x-ray spray therapy to the trunk anteriorly and posteriorly to discover whether reducing the white-cell count would affect the heart block and pulse. Consequently this treatment was given on February 4, 17 and 25 and March 8. As a result, the white-cell count dropped to 7800, where it remained until May 24, when it was 11,800. During this time, even though the white-cell count was diminished to normal, the pulse remained at 48, although on two occasions after exertion it rose to 72 for a few minutes. The blood pressure remained at 200/100 until May 24, when it rose to 270/90. The patient had felt faint with considerable abdominal distress and was acutely conscious of her heart beat. She stated she had felt best after she had had x-ray therapy of the heart and when the heart was not in block.

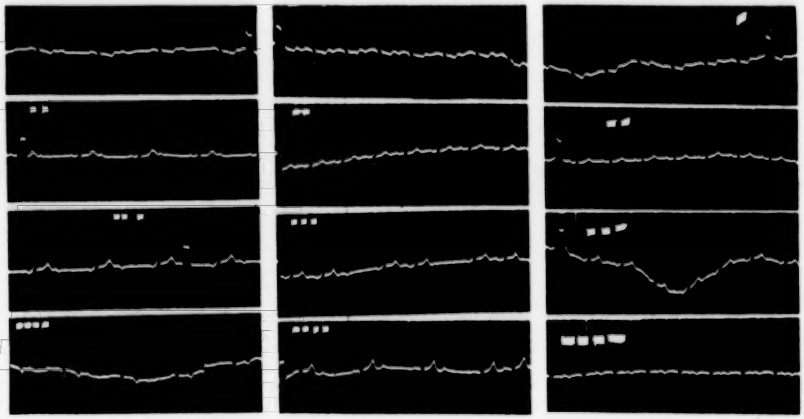

FIGURE 1. *Electrocardiographic Changes after X-ray Therapy.*

The tracings on the left, taken on August 11, before treatment, show 2:1 heart block with an auricular rate of 84 and a ventricular rate of 42. The middle tracings, taken on August 14, after treatment, show that the heart was in and out of block, normal sinus rhythm alternating with 2:1 block; T_4 is upright. The tracings on the right, taken on August 19, show normal rhythm with a rate of 77; T_4 is inverted. In all sets, there is evidence of left-axis deviation.

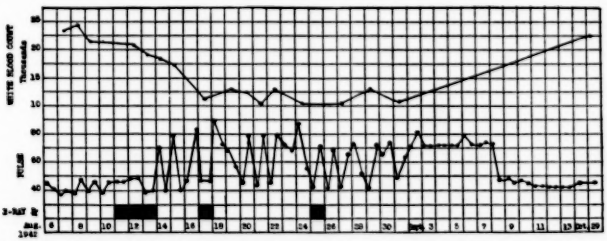

FIGURE 2. *Effect of X-ray Therapy of the Heart on the Pulse and White-Cell Count.*

The black blocks represent the dates on which x-ray therapy of the heart was given. The pulse rate had previously varied from 36 to 48 for a period of five months.

On May 29, the blood pressure rose to 300/100 and a right hemiplegia occurred. The patient became unconscious and died within 3 hours.

Comment

This was an interesting case, with hypertension and with severe and frequent headaches for many years, for which the patient took a great deal of Pyramidon. In March, 1941, it was found that she had myelogenous leukemia, which readily responded to spray x-ray therapy to the trunk anteriorly and posteriorly. A year later, the patient developed a 2:1 heart block that persisted for five months. It was believed that this block was due to a leukemic infiltration or nodule involving the bundle of His. Consequently, x-ray therapy was directed to the heart and the heart block disappeared intermittently for seventeen days and then persistently for seven days. When the heart block reappeared and persisted again for over two months, x-ray therapy was applied to the heart, and again the heart block disappeared intermittently for a month and then persistently for twenty-three days. The heart block then reappeared, and a month later when the white-cell count was 24,900 x-ray therapy was given to the trunk. Although the white-cell count remained at a normal level for three months, the heart block persisted. It is known that heart block may appear and disappear without obvious cause. The results in this case, however, strongly suggest that x-ray therapy applied directly over the heart, by its effect on a leukemic infiltration of the heart, which involved the conduction mechanism, caused the heart block, which had been present for five months, to disappear on two occasions.

Leukemic infiltrations in the myocardium are not uncommon and rarely lead to alteration in the mechanism of the heart action.[1] Leukemic infiltrations may, however, produce, besides diffuse infiltrations, definite nodules resembling tumor metastases,[2, 3] and cardiac arrythmias may occur in tumors of the heart.[4, 5]

The cause of the leukemia in this case is unknown, although one son, a physician, believed that it was due to the long-continued use of large doses of Pyramidon. A report in relation to Pyramidon was made by Delore and Borgomano,[6] who observed leukemia in a worker who for five years had extracted Pyramidon with benzene; the disease may have been due to the Pyramidon rather than to the benzene.

Summary

This paper reports the case of a woman who had hypertension for twenty years and leukemia for two years. For five months she had a 2:1 heart block that was believed to have been due to a leukemic nodule or infiltration involving the bundle of His. X-ray therapy applied to the cardiac area was followed by a disappearance of the heart block for several days on two occasions. Finally, on a third occasion when the white-cell count was elevated and the heart was blocked, x-ray therapy applied to the trunk did not cause the heart block to disappear even though the white-cell count was reduced to normal.

It is suggested that x-ray therapy of the heart caused the heart block to disappear by its effect on a possible leukemic infiltration of the heart that involved the conduction mechanism.

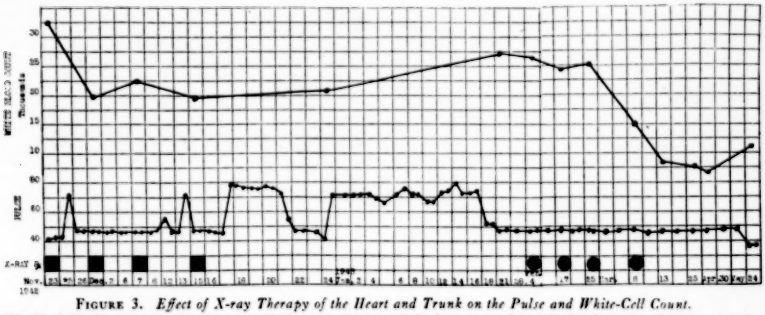

Figure 3. *Effect of X-ray Therapy of the Heart and Trunk on the Pulse and White-Cell Count.*
The black blocks represent the dates on which x-ray therapy of the heart was given; the black circles, the corresponding dates for x-ray therapy of the trunk. For ten weeks previously, the pulse had varied from 42 to 48.

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MEDICAL PROGRESS

SPONTANEOUS, THREATENED AND HABITUAL ABORTION: THEIR PATHOGENESIS AND TREATMENT*

ARTHUR T. HERTIG, M.D.,† AND ROBERT G. LIVINGSTONE, M.D.‡

BOSTON

SPONTANEOUS abortion, together with its intimately related syndromes of threatened and habitual abortion, is a frequent and therefore important complication of pregnancy. A voluminous literature not only attests to these facts but also emphasizes the general biologic complexity of the condition.

That man is not the only species subject to this complication of pregnancy is shown by studies on embryonic pathology in mammals (Corner[1]). Thus, the domestic sow shows a fairly constant ovular mortality of approximately 30 per cent, as judged by the discrepancy between the number of ovulated ova — based on counts of corpora lutea — and the number of such potentially fertilizable ova that reach full term as viable living fetuses. A similar situation obtains in laboratory animals such as the rat, rabbit and ferret. A comparable ovular mortality has been postulated in domestic animals, such as cows and mares, that ordinarily liberate but one ovum at the height of estrus. It has long been known that a normal pregnancy does not necessarily result from the single mating of a known fertile pair of such domestic animals. Such failures, according to Gowan,[2] may amount to 20 to 25 per cent in beef and dairy cattle, and are ascribed to disasters that may overtake the ovum at any time from its ovulation through fertilization and subsequent development. Approximately one third of the 30 per cent defective ova in animals that produce litters, constituting about 10 per cent of the total number of ova thus liberated, reach a stage in their development that coincides with a clinically recognizable pregnancy. The other two thirds, or 20 per cent of all ovulated ova, may fail to become fertilized, to undergo segmentation or to implant. Thus, the 10 per cent that do implant and that develop to a variable degree but ultimately die before full term are closely analogous to the 10 per cent (approximately) of human pregnancies that end in abortion.

Rock[3] in a review published in this journal in 1940 summarized all the essential aspects of abortion. It is the purpose of the present article to stress the pathogenesis of spontaneous abortion and to summarize the recent literature with respect to the treatment of the theoretically preventable forms of this condition, namely, threatened and habitual abortion. Stated differently, it is an attempt to trace the various pathologic stages leading up to a spontaneous abortion and to determine what proportion of such abortions are treatable, at what stage in their development such treatment must necessarily be instituted to save the pregnancy and what constitutes modern methods of treatment.

It is apparent that any spontaneous abortion goes through various stages, including the threat to abort as evidenced by bleeding and uterine cramps, and progresses ultimately to an inevitable abortion that may be either complete or incomplete. It is furthermore evident that during this stage, when the patient is threatening to abort, it may be difficult or impossible to determine clinically whether or not the pregnancy can be salvaged. Hence, all threatened abortions must, in the absence of more precise clinical signs, be considered salvageable until proved otherwise. A certain proportion of such abortions, however, subside without any specific treatment other than bed rest and mild sedation, the remainder being completed. The latter pregnancies are therefore the only ones that yield information about the causes of abortion. In a large proportion of cases, pathological examination of such abortuses gives a definite clue as to the cause of the abortion. My[4] analysis of 1000 abortuses forms the basis for the statements on the pathogenesis of spontaneous abortions.

It is evident that any rational treatment of threatened or habitual abortion must be directed toward saving the pregnancies that are fundamentally salvageable when the patient is first seen, even though the physician does not at that time know whether or not such a pregnancy can be saved. For this reason, the results of the treatment of threatened and spontaneous abortion reported in the literature should be interpreted in the light of the foregoing, for it must be stressed that a certain proportion of such patients will not abort anyway and a certain proportion will abort no matter what the treatment. The percentage of successfully treated threatened and habitual abortions must therefore consist of the group of pregnancies that

*From the Boston Lying-in Hospital and the Departments of Pathology and Obstetrics, Harvard Medical School.

†Assistant professor of pathology and of obstetrics, Harvard Medical School; pathologist to the Boston Lying-in Hospital and the Free Hospital for Women, Brookline; obstetrician to outpatients, Boston Lying-in Hospital.

‡Former house officer, Boston Lying-in Hospital.

would not have aborted anyway, in addition to those that are salvageable when the patient is first seen. This percentage would be ascertainable if the various factors were known. Unfortunately, at the present time not all such factors are known, or at least agreed on, by the various authors writing on the subject.

Incidence

Spontaneous Abortion

It is generally agreed by most authors that by a conservative estimate 25 per cent of pregnancies end in abortion of induced, therapeutic or spontaneous origin.[3] The latter cause accounts for one third of the total group, or approximately 8 per cent of all pregnancies. Among other authors, Mason[5] and Silbernagel and Burt[6] place this figure at 6 and 13 per cent, respectively. I[7] have examined pathologically all the abortuses from a large private obstetric practice in Boston over a period of six years, and have found the incidence of spontaneous abortion to be 10.6 per cent of the 1150 cases of full-term pregnancy and spontaneous abortion combined. If the cases of therapeutic abortion, hydatidiform mole and ectopic pregnancy are included in the total, the proportion of the total number of obstetric cases ending in spontaneous abortion becomes 10.4 per cent. In a report on the treatment of habitual abortion with vitamin E authorized by the Council of Pharmacy and Chemistry of the American Medical Association I[8] summarized the findings of various American authors (Plass, Brunner, Newton, Simmons and Kopp) and concluded that 9.8 per cent of all pregnancies terminate in spontaneous abortion. It seems fair, in view of the foregoing data, to assume that approximately 10 per cent of all pregnancies abort spontaneously.

Threatened Abortion

In order to evaluate properly the results of the treatment of threatened abortion, it is necessary for the physicians who treat it to have a uniform concept of what the condition is. Unfortunately, not all therapeutic reports in the literature appear to define threatened abortion in the same terms. For example, Mason[5] and Soule[9] consider hemorrhage or uterine cramps or both to constitute a threat to abort, whereas Silbernagel and Burt[6] state that a threatened abortion is always accompanied by uterine bleeding, either with or without uterine cramps. Rutherford[10] required that the patient pass an amount of blood by vagina — excluding cervical and vaginal lesions — sufficient to make a stain 5 cm. in diameter on a vulvar pad before the case was classed as a threatened abortion. It seems by a priori reasoning that the threat to abort is less serious if the patient merely has uterine cramps instead of uterine bleeding, either with or without cramps. Hence, the results of any therapy in the first group may reasonably be expected to be better than those in the second group.

The incidence of threatened abortion is variable, as one would expect from such variations in the concept of the condition. It occurred in 0.94 per cent of 24,289 pregnancies at the New York Hospital (Javert and Stander[11]) over a period of eight and a third years. Paine[12] states that 3.8 per cent of the patients at the Evangeline Booth Hospital in Boston threatened to abort, a figure that is in essential agreement with that of Rutherford[10] of 4.0 per cent for the Boston Lying-in Hospital.

Since all patients who ultimately abort must necessarily threaten to abort for a variable period before they complete the process, the true incidence of threatened abortion must be at least as great as the incidence of spontaneous abortion. In the light of this fact, and considering an accepted incidence of 10 per cent for spontaneous abortion, the incidence of threatened abortion appears to be surprisingly low. This discrepancy is rationalized only when one considers the incidence of threatened abortion in private practice. Silbernagel and Burt[6] state that 140 (16 per cent) of their 870 private obstetric patients threatened to abort, whereas 10.9 per cent of Mason's[5] private patients did so. The only explanation for this discrepancy between the figures of large obstetric hospitals and those of private obstetric practitioners lies in the fact that private patients consult their physicians much earlier in pregnancy than do a comparable group of clinic patients. Hence, many of the potential clinic patients who are only two to three months pregnant have threatened to abort, and indeed have carried out that threat before coming to the hospital for their initial visit. That this assumption is true is shown by the frequency with which clinic patients give a history of having had a previous abortion at home and having consulted their physician or hospital, if at all, only because of continued bleeding due to incompletion of the abortion.

If it is difficult to obtain uniformity of opinion on what constitutes a threatened abortion and on how frequently the condition actually occurs, it is even more difficult to obtain figures that are in uniform agreement regarding the prognosis of the pregnancy when once it threatens to abort. Irving[13] states that over half the patients who threaten to abort ultimately go to term and deliver normal babies. Other authors, however, are by no means so sanguine in their outlook. Thus, Javert and Stander[11] found that 100 per cent of their untreated threatened aborters aborted. Silbernagel and Burt[6] found that only 6 per cent of their untreated threatened aborters went to term, whereas 24 per cent of Rutherford's[10] 91 cases failed to abort.* Parish[14] and Falls and his co-workers[15] are in rela-

*It must be pointed out, however, that endometrial biopsies were taken from the lower uterine segment of these patients in an attempt to determine the state of the endometrium and thus gain some idea of the inevitability of the abortion. The concept back of this study was based on my continued observation over a number of years that all abortuses show a marked degree of decidual sinusoidal thrombosis, with resultant decidual necrosis and hemorrhage. It was argued that, with the presence of this triad of pathologic signs, the prognosis for a pregnancy was poor — even though the ovum had not yet aborted.

tively close agreement that 57 and 39 per cent, respectively, of their control cases of threatened abortions go to term. Walsh, in discussing Paine's[12] paper, makes a general statement that nearly half the threatened abortions are saved. Bach and Winkler,[16] according to an abstract in the *Journal of the American Medical Association*,[17] state that 50 (65 per cent) of their 74 control cases of threatened abortion continued to term. Some doubt may be cast on this figure, because in another abstract[18] of the same article the title is slightly different and includes cases of habitual as well as threatened abortion.

It appears that such a variation in the prognosis of untreated threatened abortion will have to be rationalized and an agreement reached on what the true prognosis of untreated threatened abortion is before the real worth of various specific therapies for this condition can be evaluated.

Habitual Abortion

This condition, according to the report of the Council on Pharmacy and Chemistry of the American Medical Association,[8] "is defined by Bishop as premature delivery on more than one occasion before the fifth month of gestation not due to discoverable disease, organic cause or artificial induction." This concept is not entirely in accord with mine, since it is possible to have recurrent spontaneous abortion caused by discoverable disease and an organic factor, as will be shown later in the section on pathogenesis. A more rational approach to the problem would be to consider a true habitual aborter as one who "has had at least two consecutive abortions."[8] If this last definition is further clarified to include the phrase "two consecutive spontaneous abortions," I shall be in perfect accord with it.

The incidence of habitual abortion may be expressed in terms of its proportion of total pregnancies or as a simple percentage of all spontaneous abortions. Thus, the incidence given by Bishop[8] is 0.41 per cent of a series of 2687 pregnancies, whereas Malpas's[19] comparable figure is 1.0 per cent. In Javert and Stander's[11] series of 1648 abortions admitted to the New York Hospital, 59 (3.6 per cent) of the patients gave a history of having had three or more abortions. It is not evident from the latter author's data what proportion of either the habitual or the total series of abortions were induced. If one admits that 35 per cent of all abortions are spontaneous in origin (see above) and assumes that all these 59 cases were true spontaneously recurrent abortions, 9.8 per cent of the total number of Javert and Stander's spontaneous abortions were due to recurrent causes. Actually, the proportion of habitual abortions in all spontaneous abortions probably lies somewhere between the 3.6 and 9.8 per cent. Similarly, if Bishop's[8] figure of 0.41 per cent as representing the absolute incidence of habitual abortion in pregnancy is used and it is realized that 10 per cent of all pregnancies abort spontaneously, the proportion of spontaneous abortions that are due to recurrent factors is 4.1 per cent. These figures are in general agreement with the conclusion in the report of the Council on Pharmacy and Chemistry,[8] based on Whitehouse's[20] data, "Although the diagnosis of repeated abortion might have been made in from 4.5 to 6.8 per cent of the cases considered in this analysis, it seems likely that at least 2.9 per cent of the women were liable to repeated abortion and possible that 7.7 per cent may have been subject to the probability of abortion as great as 0.84."

Pathogenesis

Threatened Abortion

There are no definite statements in the literature concerning the underlying pathologic anatomy of this condition. It seems logical, however, to assume that the endometrium shows the same fundamental picture as in spontaneous abortion, namely, thrombosis of decidual sinusoids with resultant necrosis of and hemorrhage into the decidua. The degree of this process is probably not so marked in threatened as in spontaneous abortion.

These assumptions on my part are based on observations made on the endometrium (decidua) of therapeutically removed early pregnant uteri at the Boston Lying-in Hospital and the Free Hospital for Women. Beneath the developing placentas of such pregnancies one almost invariably encounters a small area of necrotic decidua with its associated thrombosed sinusoids. Thus, there exists even in anatomically normal pregnancies a mechanism that may lead to bleeding from the placental site and hence cause the clinical syndrome of threatened abortion.

The cause of this disturbance in the placental site of a normal pregnancy, which is beyond the scope of this paper, is probably the continual encroachment of the growing placenta on the endometrium of the placental site. It is probably a matter of chance, therefore, whether the necrosis is extensive enough to cause bleeding and, if so, whether the blood will escape into the vagina and thus become clinically evident. It becomes apparent, in the light of these observations, that not all uterine bleeding necessarily means an inevitable abortion; nor, on the other hand, does it surprise one that a significant percentage of spontaneous abortions may produce anatomically normal ova that are salvageable if proper treatment is instituted in time.

Spontaneous Abortion

The data in the subsequent section are a summary of an analysis of 1000 spontaneous abortions and

miscarriages examined pathologically at the Boston Lying-in Hospital during a six-year period. The original data were published by me[4] in collaboration with Sheldon in 1943.

During this study it became apparent that two main factors were operating to produce a spontaneous abortion, namely, those traceable to defects or abnormalities of the ovum and those due to maternal causes. In the former category were 617 abortuses, or 61.7 per cent of the series, whereas the remaining 383, or 38.3 per cent, were in the latter category.

It is obvious that, no matter how detailed is the pathological examination of the abortus or how perfect is the clinical history, — which many histories in this series were not, — this approach to the problem of spontaneous abortion is subject to error. Some of the interpretations, therefore, may be open to question. This is so if only for the reason that the pathological study of the abortus alone leaves out one, if not the most important, aspect of the problem — the pathological examination of the uterus. Furthermore, these studies are not correlated with any associated endocrinologic studies of the patient — another important aspect of the problem. Be that as it may, they furnish some clue to the essential problem in the pathogenesis and treatment of spontaneous abortion; namely, what sort of ova spontaneously abort and how many of them could theoretically have been salvaged when the patient was first seen by the physician.

Ovular factors. The largest single group of causes of spontaneous abortion is that which results in the production of a blighted or pathologic ovum: that is, one in which the embryo is absent or extremely defective. In this category were 489 abortuses, or 48.9 per cent of the total number. This over-all classification does not take into account the bitter controversy that has raged for years regarding the factor or factors that cause these ova ultimately to become pathologic. It is not within the scope of this article to decide whether all these ova were defective from the beginning (germ-plasm defects) or whether one or more environmental factors acted on a normal fertilized ovum, causing it to become pathologic. Suffice it to say that my studies with Rock[21] have shown that intrinsically pathologic human ova exist soon after implantation. Four such specimens, together with an abnormally implanted but otherwise normal ovum, have been recovered from surgically removed uteri prior to the first missed menstrual period. Each of these specimens was yielded by patients who had previously had several normal pregnancies. Their fertility, therefore, had been established and general abnormalities of uterine environment ruled out.

Aside from the fact that this group of blighted ova constitutes almost half the abortuses examined, an additional fact of importance is that approximately two thirds of these ova showed variable degrees of hydatidiform degeneration of their chorionic villi.[22] In rare cases such ova, tending to abort in their tenth week of gestation, for reasons not understood, remain in the uterus and become a classic hydatidiform mole. This fact must be kept in mind in treating any case of threatened abortion, for the physician may unwittingly convert an inevitable abortion of such a pathologic ovum into a true hydatidiform mole. The probability of such an occurrence is remote, but it is nevertheless possible. One such patient, who had been treated for threatened abortion for the previous six months by a local physician, came to the Boston Lying-in Hospital and was delivered of a hydatidiform mole. The chance that this mole might have developed spontaneously cannot, of course, be ruled out.

In the series of abortuses under consideration, there were 32 (3.2 per cent) that showed localized anomalies — usually of the nervous system. That such anomalies are not incompatible with a full-term delivery and even some degree of extrauterine life cannot be gainsaid. The incidence of such anomalies was, however, four times as great as is the incidence of such anomalies in full-term deliveries at the Boston Lying-in Hospital. With these facts in mind, it is well for the physician treating threatened abortion to remember the additional possibility of bringing to term a monster that would otherwise have aborted.

Javert and Stander,[11] in commenting on this problem, state that although infants born of mothers who have threatened to abort are not necessarily malformed, the tendency may be greater than otherwise. Thus, Kotz et al.,[23] quoted by Javert and Stander,[11] gives 4.9 per cent as the percentage of malformed fetuses born to a group of mothers treated for threatened abortion, whereas these authors[11] found that in 27,000 deliveries at the New York Hospital only 2.95 per cent of the infants were so afflicted. Greenhill[24] found the average incidence of fetal abnormalities in twenty-six clinics to be only 0.94 per cent. The same author, however, found that forty clinics showed an average of 2.75 per cent fetal abnormalities in cases of placenta previa. In the light of these various data, it appears that treated cases of threatened abortion run an increased risk of producing a malformed infant, although Shute,[25] quoted by Silbernagel and Burt,[6] denies that such a mother runs an increased risk.

Various abnormalities of the placenta, all associated with normal embryos, constitute 9.6 per cent of these 1000 abortuses. Various derangements of placental formation and function are found in this group, but the commonest ones are the circumvallate placenta (4.5 per cent), hypoplasia of the placenta (2.0 per cent) and the so-called "Breus's mole" (1.9 per cent) — the latter a normal placenta in which the maternal blood has clotted, thereby causing fetal death.

The common denominator with respect to the cause of the abortion in most of these abnormalities, as well as in the remaining ones of the group (3.2 per cent), is fetal death. Some of the circumvallate placentas, however, when they separate prematurely at their margin, cause the onset of premature labor, which results in the delivery of a living but nonviable fetus.

Since most of the abortuses in all three of these major groups of ovular abnormalities could not have been salvaged, because fetal absence, deformity or death initiated the train of signs and symptoms that brought the patient to the physician, any form of therapy would have been useless. It is manifestly impossible to determine clinically which threatened aborters are going to abort and, if they are destined to do so, which of the abortuses can theoretically be salvaged. It is therefore necessary to treat all patients threatening to abort until either they become symptom free or their abortion becomes inevitable.

Maternal factors. In the next group of abortuses, those associated with maternal causative factors, there are a number of cases in which the pregnancy might have been salvaged. The criterion on which this assumption is made was the presence of a normal, living fetus at the time the patient was first seen by the physician.

The group of criminal abortions is necessarily small and constitutes 2.1 per cent of the total. It is to be expected that criminally induced abortions would not be numerous in a group of spontaneous abortuses submitted to the pathologist in an attempt to discover the cause of the abortion. I have, however, been interested in the pathologic sequence of events in criminally induced abortions and have attempted to acquire such material, thus accounting for the few cases of this type among the group of otherwise spontaneous abortions. The figure of incidence is therefore entirely erroneous and actually much lower than exists throughout the country. Suffice it to say, for the sake of comparison, that the pathologic picture is often one of premature rupture of the membranes, followed by acute bacterial inflammation of the chorion, amnion, placental villi and decidua.

Uterine abnormalities constituted 6.4 per cent of the total. Low implantation of the placenta* accounted for the vast majority of these cases (5.6 per cent of the entire 1000). Other causes of abortion embraced such diverse factors as placenta accreta, bicornuate uterus, multiple leiomyomas and fixed retroversion of the uterus. In spite of the fact that all these fetuses within the low-implanted ova were normal and many were living when the patient was first seen, the practical difficulties of prolonging the pregnancy to a time when the fetus becomes viable are obvious. These difficulties, furthermore, do not include the later ones associated with the management of placenta previa. Comment has already been made on the increased incidence of fetal abnormalities associated with placenta previa.[21] Doubtless these are due to interference with the oxygen supply and other vital factors during the early critical period of embryonic growth.

Febrile and inflammatory disease, a small but important group, constituted 2.0 per cent of the total series and included local bacterial inflammation of the endometrium, both acute and chronic, as well as general febrile states from various causes. The commonest cause of abortion in this group was acute bacterial endometritis (1.3 per cent). Fever of unknown etiology (0.5 per cent) was the next commonest cause, and such diverse causes as smallpox, chronic endometritis and pyelitis each caused one abortion (0.1 per cent). That general febrile states can and do cause spontaneous abortion is attested by the number of pregnant patients who aborted during the influenza epidemic of 1918–1919.

It is worthy of comment that local inflammation plays a relatively small part in the etiology of spontaneous abortion. This is in contrast to the views advanced in 1921 by Mall and Meyer,[26] who ascribed to inflammation a prominent role in the causation of abortion. It appears that they misinterpreted the leukocytic response to sterile decidual necrosis following thrombosis of sinusoids — a universal finding in all spontaneous abortions of whatever etiology.

A small and heterogeneous group (1.2 per cent) is formed only as a matter of convenience. It includes such diverse causes as radiation effect on ovaries (0.2 per cent), erythroblastosis fetalis (0.3 per cent), surgical removal of a corpus luteum (0.4 per cent), blood dyscrasias (0.1 per cent) and interference with the circulation of the umbilical cord (0.2 per cent).

These cases require little comment other than to note that some of them (the previously radiated cases), probably could not have been salvaged, whereas others, such as those due to surgical removal of the corpus luteum, offer ideal situations in which to employ the substitution therapy of progesterone injection.

Patients with anatomically normal ova constituted 26.6 per cent of the entire series. Since a large number of them — approximately two thirds — possessed not only normal but living fetuses when first seen by the physician, it is within this group that hope for successful therapy lies. Because of the importance of this group, the various factors apparently concerned are listed in some detail (Table 1).

For a detailed discussion of this group the reader is referred to the original paper[4] in which these data first appeared. Suffice it to say that even

*It may be questioned as to why low-implanted placentas should be considered as due to any maternal factor. The reason for assuming this as yet unproved relation is the high incidence of placenta previa in multiparas. It seems unlikely that the fertilized ovum of a multigravida is at all different from that of a primigravida, although the post-partum uterus of the once gravid patient never quite involutes back to its nulliparous state. The causation of placenta previa must therefore lie somewhere in the maternal realm rather than in the ovular.

though two thirds of these fetuses were macerated at the time of the abortion, nearly half were living when the symptoms or signs or both that brought the patient to the physician began. This fact is determined by knowing the date on which such symptoms or signs began and by calculating the

TABLE 1. *Classification of Cases with Anatomically Normal Ova.*

CLASSIFICATION		NO. OF CASES
Anatomically normal ova without disease:		227
Fetus macerated	146	
Fetus living	81	
Acute chorionitis, consistent with spontaneous premature rupture of membranes:		14
Fetus macerated	9	
Fetus living	5	
Positive Hinton and Wassermann tests (syphilis probably not responsible for abortion)		3
Infarction of placenta, extensive (all fetuses macerated)		1½
Toxemia of pregnancy:		5
Fetus macerated	3	
Fetus living	2	
Trauma		
Internal:		
Two successive endometrial biopsies on sterility patient not known to be pregnant		½
Exploratory laparotomy		1
Intrauterine injection of lipiodol 7 weeks prior to last menstrual period		1
External:		
Automobile accident (a *bona fide* cause of this abortion)		1
Total		266

menstrual age of the fetus from the classic tables of Streeter.[27] By this means it is possible to determine whether the fetus was younger or older than the duration of pregnancy when bleeding first began. If the former was true, the fetus was dead prior to the onset of bleeding, whereas if the latter proved to be the case, the fetus was living after the onset of bleeding. It becomes evident, therefore, that two thirds of these pregnancies with normal ova were theoretically capable of being salvaged instead of merely the apparent one third that showed living fetuses at the time of the abortion.

Considering all types of abortuses in which there was a normal, albeit sometimes a dead, fetus at the time of abortion, it is apparent from these figures that 47.9 per cent of this series of 1000 cases could be so classified. Furthermore, if one applies to this group the rough theoretical salvage rate of two thirds of such cases, one finds that one third of all spontaneous abortions contain a normal living fetus at the time the patient is first seen. This is perhaps erring in favor of the therapeutists, although the figure is not far from the actual truth. It is from such a group of cases, together with those of threatened abortion that would not have aborted anyway, that one must draw the group of successfully treated threatened aborters. It is difficult to see how a successful case could come from any other group unless, perchance, it came from the group about which there might be differences of opinion whether it really contained *bona fide* cases of threatened abortion.

Habitual Abortion

Few data exist on the pathogenesis of habitual abortion other than those contained in such a series as that discussed above in the section on spontaneous abortion. What data exist in my series can be summarized by saying that the causes of habitual abortion are apparently as varied as those resulting in a chance or single spontaneous abortion. Correlated with the clinical definition of the disease, as one resulting in two successive spontaneous abortions, is the repetition of pathologically identical or similar causes in successive abortuses. Thus, in a series of 14 patients, each of whom had two successive spontaneous abortions that were examined pathologically, each pair of abortuses appeared to have occurred following the same or similar causes. A habitual aborter, therefore, is a patient who tends to repeat a given clinicopathologic syndrome rather than to experience it only once.

Because of this fact, the problem of treating habitual abortion has at least some justification for being approached optimistically by the physician. If the patient is a known habitual aborter, it is at least theoretically possible to determine something of the probable cause or causes of future abortions and to set about treating the condition at the time of conception — an advantage not possessed by the physician treating a threatened abortion which may, from the beginning of signs and symptoms, be inevitable.

TREATMENT

This section concerns the treatment of threatened and habitual abortion only, since, once the abortion has become inevitable or is in the process of taking place, treatment becomes a matter of emptying the uterus as quickly and as safely as possible.

The problems of treating threatened abortion and habitual abortion seem to be essentially different. In the former instance, efforts are directed at stopping the uterine bleeding and associated cramps, when present. In the latter, one seeks to prevent the various and often quite diverse factors that have contributed to the previous abnormal pregnancy. Thus, the treatment of the one is essentially an emergency procedure, whereas that of the other is, or should be, an elective procedure, preferably begun before conception. Actually, when one examines the results of treatment as shown in the various published series of cases (Table 2), it appears that the same method of treatment may be equally successful whether the case be one of threatened or of habitual abortion. The only difference appears to be the stage in the pregnancy at which the treatment was started and the dosages of therapeutic agents used.

Table 2 presents the data in series of cases of threatened and habitual abortion reported by various authors, including the methods of treatment and the results. It is impossible in such a table to give details of treatment, for which the reader is referred to the original articles. In the cases listed under habitual abortion there had been

two or more successive abortions, so far as could be determined, cases stated as having had only one previous abortion being excluded. Some authors, however, did not give the number of previous abortions, and their cases may or may not have been those of true habitual abortion. The numbers of treated cases in the reports including a statement of two or more successive previous abortions are followed by an asterisk.

The therapeutic agents listed in Table 2 deserve comment, and the following is a brief outline of the dosages and the methods of administration.

Anhydro-hydroxy-progesterone (Pregneninolone — Ciba, Pranone — Schering). The oral dosage in threatened abortion is 10 to 100 mg. daily in one or divided doses for a period of three days to several weeks; that in habitual abortion is 10 mg. twice weekly. This synthetic progestational principle is said by Krohn and Harris[42] to be one sixth as effective as progesterone. It is not, however, identical in its action on the uterus (Burge and Holloway[28]). Progesterone is antagonistic to Pituitrin, whereas anhydro-hydroxy-progesterone is not.

Wheat-germ oil (vitamin E). The oral dosage is 30 to 45 cc. in the first twenty-four hours in divided doses, and 4 to 6 cc. daily thereafter until the eighth calendar month (Collins[21]).

Synthetic vitamin E (Alphatocopherol — Squibb). The oral dosage is up to 30 mg. daily and up to 240 mg. monthly in divided doses.

TABLE 2. *Summary of Data on the Treatment of Threatened and Habitual Abortions.*

SENIOR AUTHOR	THREATENED ABORTION		HABITUAL ABORTION		TREATMENT
	NO. OF CASES TREATED	NO. (PERCENTAGE) SUCCESSFULLY TREATED	NO. OF CASES TREATED	NO. (PERCENTAGE) SUCCESSFULLY TREATED	
Burge[28] (1941)	3	1 (33)			Anhydro-hydroxy-progesterone
Buxton[29] (1940)			5*	4 (80)	Progesterone
Campbell[30] (1940)			13*	11 (85)	Progesterone
Huber[30] (1940)			15*	14 (93)	Corpus luteum hormone
Singleton[30] (1940)			3*	2 (67)	Vitamin K (young grasses)
Collins[21] (1940)	24	21 (88)	12	9 (75)	Vitamin E (wheat-germ oil), progesterone and thyroid
Currie[32] (1937)	15	14 (93)	37†	35 (95)	Vitamin E (wheat-germ oil)
Davis[33] (1942)	30	17 (57)	16	8 (50)	Anhydro-hydroxy-progesterone or progesterone and thyroid
Elden[34] (1938)			8	6 (75)	Progesterone
Ehrhardt[35] (1936)			2	2 (100)	Placental extract
Falls[36] (1936)			41	34 (83)	Progestin
Falls[18] (1942)	217	189 (83)	59	51 (86)	Lutein
	234	206 (88)	63	58 (94)	As above
	61	53 (87)	55	51 (93)	As above
Hamblen[37] (1941)	1	1 (100)			Estriole glucuronide, anterior-pituitary-like hormone and progesterone
Hamblen[37] (1941)			5*	1 (20)	Progesterone, estriole, anterior-pituitary-like hormone and thyroid
Hirst[38] (1918)			3*	2 (67)	Corpus luteum extract
Javert[11] (1943)	10	8 (80)	14*	13 (93)	Vitamins C and K, thyroid, progesterone and various minerals
Kane[39] (1936)			40	36 (90)	Proluton, thyroid and sodium iodide
Karnaky[40] (1942)	16	16 (100)			Stilbestrol
Kotz[23] (1941)	139	64 (46)	42	37 (88)	Progesterone
Krohn[41] (1935)	11	9 (82)	8	5 (63)	Progestin
Krohn[42] (1941)	39	32 (82)	11	10 (91)	Anhydro-hydroxy-progesterone and barbiturates
Lubin[43] (1941)	15	13 (87)	7*	5 (71)	Vitamin E (synthetic)
Malpas[19] (1938)			7*	2 (29)	Vitamin E (wheat-germ oil)
Malpas[19] (1938)			4*	2 (50)	Progestin
			33*	20 (61)	Organic arsenicals
Mason[44] (1938)			3*	3 (100)	Anterior-pituitary-like hormone (pregnancy urine extract)
Mason[5] (1942)	34	30 (88)	17	15 (88)	Progesterone
McCord[45] (1937)			3*	3 (100)	Progestin
Olson[46] (1943)	167	91 (55)			Various (opiates, barbiturates, atropine, vitamin E, progesterone and thyroid)
Posner[47] (1941)			1‡	1 (100)	Vitamin E (wheat-germ oil) and progesterone
Rosenfeld[48] (1938)			20	19 (95)	Pregnancy serum (500 cc. weekly throughout pregnancy)
Schneider[49] (1942)	24	12 (50)	16*	16 (100)	Estrogens or progesterone
Schneider[50] (1942)	2	2 (100)			Estrogens or progesterone
Shute[51] (1942)	46	35 (76)			Vitamin E (wheat-germ oil)
Soule[9] (1941)	16	12 (75)			Anhydro-hydroxy-progesterone or progesterone, or both, and thyroid
Stähler[52] (1941)			14*	13 (93)	Vitamin E (synthetic) and progesterone
Vogt-Möller[53] (1933)			20	17 (85)	Vitamin E (wheat-germ oil)
Vogt-Möller[54] (1936)			56	38 (68)	Vitamin E (wheat-germ oil)
Watson[55] (1936)	15	11 (73)	28*	21 (75)	Vitamin E (wheat-germ oil)

*Stated to have had two or more previous successive abortions.
†Stated to have had two or more previous abortions, but not whether successive.
‡Eight previous successive abortions, and hence worthy of inclusion, even though only a single case.

Thyroid. The oral dosage is 6 to 30 mg. (1/10 to 1/2 gr.) two to three times daily.

Progesterone. Doses varying from 1/25 rabbit unit to 10 mg. have been given intramuscularly. The average dose for bleeding is 2 to 10 mg. Soule,[9] whereas the prophylactic dosage is 1 mg. every three or four days for a variable length of time but occasionally through the sixth month.

Diethylstilbestrol. The dosage in threatened abortion (Karnaky[40]) is 25 mg. injected into the anterior wall of the cervix, followed by 5.5 mg. every fifteen minutes as long as pain persists. When the latter disappears, 10 mg. is given orally every hour for six doses and then 5 mg. every hour for six doses. Following subsidence of pain and bleeding, 10 mg. is given by mouth daily until the eighth month. In habitual abortion, 10 mg. is given in a like manner as soon as pregnancy is diagnosed and is continued until the seventh month.

Lutein. This is an aqueous extract of corpus luteum (Hynson, Westcott and Dunning) whose exact composition is unknown and at present has not been completely bioassayed. Its effective strength is said by Falls[35] to be such that 1 cc. is equivalent to 1/10 unit of progesterone. In threatened abortion, Falls and his collaborators inject 3 cc. intramuscularly every four hours during active bleeding and cramping, in addition to absolute bed rest. After symptoms of bleeding and pain have subsided, 3 cc. is given daily for five to seven days and then 3 cc. twice a week until viability is reached. For habitual abortion, these authors inject 3 cc. intramuscularly twice a week.

Threatened Abortion

It is evident from Table 2 that several hundred cases of threatened abortion have been treated in a variety of ways. There is a total of nine series[5, 15, 23, 32, 40, 42, 43, 51, 55] containing 15 or more cases in which only one specific therapeutic agent was used. The latter varied from diethylstilbestrol through natural and synthetic vitamin E to preparations of corpus luteum.

These various specific agents may not be quite so diverse in their action on the pregnant uterus as appears at first glance. Thus, the metabolism of the estrogens and that of progesterone are closely correlated, as shown by the work of Smith and Smith.[56–58] A practical illustration of this correlation is the method by which Schneider[49, 50] treats his cases of threatened abortion: estrogen and pregnanediol levels are determined and the patient is given the hormone that is shown to be abnormally low. Also, the role of vitamin E in its essential relation to normal pregnancy is not yet well understood: Stähler and Kaiser,[52] Stähler and Pehl[59] and Bach and Winkler[16] cite evidence for the relation between vitamin E (synthetic tocopherols) and progesterone, whereas Shute[51] speaks of the imbalance between vitamin E and estrogens. A relation between vitamin E and iron assimilation by the fetus is indicated by the work of Simmonds, Becker and McCollum.[60] These workers ascribe fetal death in rats deficient in vitamin E to a crisis in iron assimilation that is obviated by giving vitamin E in adequate amounts at the beginning of pregnancy.

These specific agents for the treatment of threatened abortion are often used in various combinations, either with or without the addition of thyroid. The role played by the latter in pregnancy is not fully understood. That it is important, however, is shown by the increase in the abortion rate in so-called "goiter areas" (Hamblen,[61] 1943). With the adequate use of thyroid in such areas, there is a reduction in the abortion rate.

Other specific substances, such as the so-called "antihemorrhage" vitamins C and K, have recently been used in the treatment of threatened abortion by Javert and Stander.[11] In a high proportion of these authors' cases the use of these substances is predicated on the demonstrably low values of the substances themselves or of their essential end product.

The treatment of threatened abortion is centered on the problem of stopping hemorrhage and quieting the uterus. For this purpose some progestational principle is often used. Hamblen,[61] in a recent review article, thus summarizes the status of this phase of the therapeutic problem:

> Numerous reports have cited the efficacy of progestin in preventing abortion. Progestin often has received credit for success when the effects of adjuvant measures, such as thyroid substance, bed rest, limitation of sexual and other activities and so forth, have not been evaluated. We have not been impressed particularly with progesterone therapy in these conditions. Our percentage of successfully treated patients has not been as high as those of some other investigators, although the dosages were comparable or larger. When pregnant women show definite evidence of deficiency in the progestational principles, — that is, decreased pregnanediol values of the urine, — even the most intensive progesterone therapy fails to prevent abortion.

Although apparently patients with low levels of pregnanediol excretion often abort and therapeutic efforts may fail to raise the levels of this substance by progesterone administration, the administration of some potent corpus-luteum preparation, preferably progesterone, seems indicated in cases of threatened abortion with uterine cramps, since this is probably the most effective way of stopping such signs and symptoms if the abortion is not inevitable. Concerning progesterone versus other derivatives of the corpus luteum, Macht[62] cites evidence that an aqueous extract of the latter, Lutein (Hynson, Westcott and Dunning) is a potent preparation, 1 cc. of which is equivalent to 0.1 mg. of progesterone. It must be realized, however, as Buxton[29] states, that there are so many variables in progesterone metabolism and excretion that pregnanediol assays cannot indicate the degree of progestational activity.

Ideally, of course, it would be desirable to know in advance whether or not a threatened abortion is inevitable. Since this is impossible, efforts are necessarily directed at saving the third of spontaneous abortions that theoretically can be saved, even though this entails treating the remainder, which are inevitable in spite of treatment. If it is possible to determine, as does Schneider,[49, 50] which of the ovarian hormones is low in a case of threatened abortion, the low one should be administered. Otherwise, it seems well to treat the patient by some

form of corpus-luteum preparation, vitamins E, C and K and thyroid, this treatment being correlated with a program of so-called "nutritional adequacy," as advocated by Javert and Stander.[11]

That the treatment of threatened abortion is unsatisfactory at best is indicated by the variety of its causes and the present diversity of its treatment. Elucidation of these complex etiologic factors and evaluation of one or several specific therapeutic agents in various combinations await the study of large series of cases by investigators who will use the combined talents of the obstetrician, the endocrinologist and the embryologic pathologist. Until this time comes, the treatment of threatened abortion and its closely related syndrome, habitual abortion, rests on the physician's practical judgment aided by empiric uses of more or less specific substances whose action is not fully understood at the present time.

Habitual Abortion

The foregoing remarks are applicable in general to the problem of the treatment of habitual abortion. This condition differs from chance abortion in that the same etiologic factor tends to be repeated in two or more successive abortions. Such a recurrent factor is often the same as the chance or isolated factor causing a single abortion.

Treatment should begin prior to conception, because the genesis of many abortions is laid during the time before the first missed menstrual period. The same over-all treatment is indicated as is advocated above for threatened abortion, because of the present lack of more specific therapeutic knowledge. The use of progesterone or some other potent corpus-luteum derivative is indicated before bleeding and cramping begin, because of its effect on the progestational endometrium and the latter's effect, in turn, on the ovum — even before its implantation.

Vitamin E, judging from the literature, has an important effect on the favorable outcome of pregnancy in cases of habitual abortion — this in spite of the fact that the average human dietary cannot be shown to be deficient in vitamin E. Bacharach,[63] in 1940, summarized several relatively large series of true habitual abortions reported by other authors and showed that vitamin E apparently supplied the specific factor, so that patients with two, three and four previous abortions had a 75, 73 and 79 per cent chance, respectively, of a successful pregnancy. The rate of spontaneous cure in such cases if untreated, according to Malpas,[19] would have been 62, 28 and 7 per cent, respectively.

In contrast to these relatively hopeful data are the conclusions of the report of the Council on Pharmacy and Chemistry of the American Medical Association,[8] also published in 1940, which used some of the same data reviewed by Bacharach.[63] This report states that vitamin E cannot as yet be accepted owing to lack of convincing evidence, because the diagnosis of habitual abortion is open to question in these cases, because of the variation in dosage, and because not enough is known about the spontaneous cure rate in habitual abortion. Nevertheless, in my opinion vitamin E should be used because it appears to offer great hope in salvaging pregnancies that would otherwise habitually abort.

Conclusions

Threatened abortion occurs in at least 16 per cent of all pregnancies.

Spontaneous abortion occurs in approximately 10 per cent of all pregnancies.

Habitual abortion constitutes approximately 4 per cent of all spontaneous abortions.

Approximately 40 per cent of threatened abortions do not abort regardless of the treatment employed.

Approximately 60 per cent of threatened abortions abort if untreated.

On the basis of a series of 1000 cases examined embryologically and pathologically, approximately one third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician.

In view of the three preceding conclusions, approximately 60 per cent of threatened abortions under adequate treatment may fail to abort.

Threatened abortion should be treated by some potent corpus-luteum preparation or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C and K and thyroid, in conjunction with a program of so-called "nutritional adequacy."

Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to or coincident with conception.

221 Longwood Avenue

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 30261

PRESENTATION OF CASE

A sixty-five-year-old housewife entered the hospital because of abdominal pain.

The patient had been in apparent good health until 2:00 p.m. of the day before admission, one hour after a light lunch, when she was seized with severe abdominal cramps accompanied by nausea, vomiting and moderate prostration. Between then and 7:00 p.m., she had four bowel movements, the first three of which were formed, the last one semiformed. During that period she vomited about nine times, with distressing retching each time. She was seen by her physician three and a half hours after the onset of the illness. Examination showed decreased peristalsis and generalized tenderness over the entire abdomen, without localization, spasm or masses. The blood pressure was 122 systolic, 70 diastolic. The temperature was 96.5°F., and the pulse 72. The white-cell count was 10,000. In the course of the next four hours, abdominal tenderness became marked, so that any but the most superficial abdominal palpation caused marked pain referred to the midepigastrium. There was no pain in the back, shoulder or scapula. A vague mass was palpable in the left lower quadrant, and peristalsis was almost absent. The patient remained at home under the close supervision of her physician, who gave her 1000 cc. of 5 per cent dextrose in saline solution. The pain was controlled by 1/6 gr. of morphine. By midnight the abdomen had become much softer and less tender, without any distention; peristalsis was nearly normal. There was one small, liquid, pinkish bowel movement. She was quite comfortable through the night. The following morning she still had distress across the upper abdomen. She had had no chills or fever. She was admitted to the hospital.

For many years she had had a red-cell count seldom over 4,000,000, without any evidence of blood loss. This had been intermittently treated by liver. Seven years before the present illness, she had "spastic colitis." At that time, barium enemas and gall-bladder studies were negative. She had had a laparotomy and a uterine suspension thirty-three years before entry.

Physical examination on entry showed a well-developed, well-nourished, rather sick-looking patient. The heart and lungs were negative. The abdomen was not distended, and there was little real spasm. Peristalsis was almost entirely absent. The abdominal mass was not palpable. Palpation anywhere in the abdomen gave rise to pain in the epigastrium.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 99.4° F., and the pulse 80.

Examination of the blood showed a white-cell count of 17,300, with 86 per cent neutrophils. The stools gave a ++++ guaiac test. The urine was negative. A plain film of the abdomen (Fig. 1) showed a moderate amount of gas in the stomach and a small collection of gas, apparently in the dilated small bowel, which was in the midabdomen. Little gas was seen in the colon. No soft-tissue masses were visible.

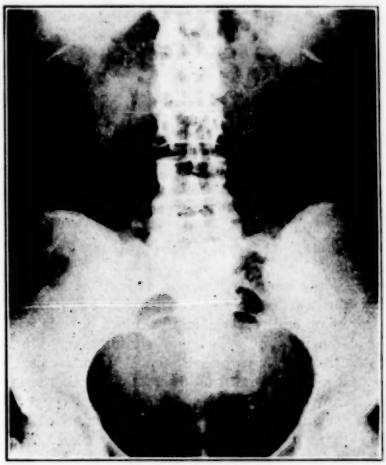

FIGURE 1. *Plain Film of the Abdomen, Showing Gas in the Small Intestine.*

The patient was given a transfusion, and a laparotomy was performed about two hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. DAVID CHEEVER†: I consider these exercises to be instructional. They are always instructional to me, so that the general level of my remarks is apt to be directed to medical students who are present or younger members of the house staff. I say that

*On leave of absence.

†Surgeon emeritus, Peter Bent Brigham Hospital

in case some of my remarks seem to be elementary at times.

"A sixty-five-year-old housewife entered the hospital because of abdominal pain." When one sees a patient or examines a protocol like this, which is essentially the same thing, I think one gets an immediate impression. I make a mental note that the patient was in the decade of life when on the whole carcinoma is most frequent, and that the patient was a woman, and therefore the possibility of disease of the pelvic viscera must be considered later.

If we can believe the history it is perfectly obvious that there was no immediate antecedent history that had anything to do with this attack. It was a sudden, acute abdominal attack. The light lunch obviously had nothing to do with it. She had severe abdominal cramps, which were obviously due to painful peristalsis, and immediate vomiting. What is the significance of these two symptoms? First, of course, by far the most frequent cause of abdominal pain with vomiting and cramps is some form of acute gastroenteritis, gastrointestinal "flu" if you like, or some functional disturbance. In other words, it would, up to that point, explain everything perhaps, and the diagnostician's chief care is to differentiate the functional disturbance of that sort, which is obviously not surgical, and an acute condition in the abdomen of a surgical nature. That is always the thing that should come to the mind of the local physician when he sees such a patient.

As to the bowel movement, it may be presumed that she was somewhat constipated and that the lower colon and rectosigmoid were full of feces when she came in, and with some stimulation of peristalsis she had three formed stools, which means the normal movement of the lower bowel, and the last one semiformed.

The vomiting is interesting. She vomited nine times with distressing retching every time. When the stomach and intestine are affected by a functional disturbance there may not be very much pain. There is apt to be vomiting and diarrhea, but once the intestine is empty that is apt to be the end of it, although the intestinal diarrhea may go on. Here is a woman who nine times had repeated retching and vomiting. We are not told whether the vomitus or the gastric contents contained bile or blood or material suggestive of jejunal contents, but we assume, inasmuch as we are not told these things, that it did not contain anything significant. I think it was one of the Mayo group who once said, among many other wise things, that the stomach was the alarm clock of the physical economy. The stomach is apt to reject its contents, and vomiting to set in, in all sorts of conditions — acute gastritis or any acute condition within the abdomen. As you well know, the emotions may cause vomiting, or it may occur at the beginning of infectious disease or with disturbance of the internal ear or a brain tumor, and so it goes. In other words vomiting must never be considered as necessarily or even probably indicative of trouble in the stomach, although that is a frequent cause. So my impression here is definite — that this vomiting was of a reflex nature due to some insult to the peritoneum of the abdominal viscera below the stomach and probably had nothing at all to do with the stomach.

Evidently this patient was not used to gritting her teeth, and waiting and suffering in silence. She sent for a doctor quite promptly. She undoubtedly was an intelligent person. From here on there is mentioned a number of times the type and degree of peristalsis noted. Some of the gentlemen here may have devoted themselves to the study of peristalsis. Personally, I do not believe that much significance can be attached to the determination of peristalsis, except very broadly; if we examine the abdomen and find absent peristalsis we may assume that in all probability the situation of paralytic ileus exists. The prototype and usual cause is peritonitis, unless there be some toxic cause. The other is extreme peristalsis with a tinkling sound, which we hear in the early stages of acute mechanical obstruction. Between these extremes one cannot tell much about the significance of peristalsis, but evidently the group that studied this case did think there was a good deal in it, very likely something I do not realize.

Of course the degree of tenderness is extremely important but there was no localized tenderness, and no spasm, and therefore, we can confidently rule out peritonitis. Certainly we can rule out acute perforative peritonitis. Acute perforation of a hollow viscus would give exquisite localized pain, exquisite localized tenderness and boardlike spasm and rigidity — a very different thing from what we have here. The question arises, Of what significance was this tenderness? Was there any peritoneal insult? Hardly. I simply remind you of the fact that if any of you have happened to be unfortunate enough to be seasick, and perhaps have vomited nine times, with retching, you know that the belly becomes quite tender, so I do not believe that this tenderness was important; but we can say that there was no perforative peritonitis. "Abdominal tenderness became more marked, so that any but the most superficial abdominal palpation caused marked pain referred to the midepigastrium." Again we should like to know how much tenderness there was, but again we may assume that there was no marked spasm related to it. So that it does not seem to me significant. The reference of the pain to the epigastrium is extremely interesting, of course, and must be of great importance. Anatomically speaking, we think of the organs that are situated in the epigastric region. I shall not bore you with enumeration of these organs — the stomach, pylorus, duodenum, gall bladder and so forth cover some of them — but especially we must

remember that the pancreas is situated there. It is an organ that must always be considered in any acute abdominal situation. The symptoms of acute pancreatitis, the typical ones, are very characteristic; yet many a case of pancreatitis is quite obscure from a diagnostic point of view. So let us remember the pancreas.

What is the likeliest cause of the pain in the epigastrium? As we know, pain due to spasm of the small intestine as contrasted with painful peristalsis of the large intestine, is apt to be referred to the region above the umbilicus, and in the large intestine is apt to be referred to the hypogastrium, below the umbilicus, and that, as you well know, is because the sympathetic pathways from the intestine are related to certain metameres of the body — thus pain in the small intestine is associated with pain sensations referred to the distribution of the seventh, eighth, ninth and tenth dorsal nerves in the epigastrium. That is a general statement and a useful one, but of course it must be mentioned that it is frequently violated.

"There was no pain in the back, shoulder or scapula." That statement refers undoubtedly to the absence of symptoms that might have been caused by injury to the phrenic area. Also, absence of pain in the back suggests that the gall bladder was not involved.

The vague mass that was palpable we must take as something that could not be identified; its actual existence was not certain.

This patient had a very discriminating and keen physician to attend her. The notes that he makes here are those of an experienced man who has seen this type of case. One-sixth of a grain of morphine after he made the examination was necessary, and the proper treatment. One-sixth of a grain could hardly mask any important symptoms. We know that she got through the night very well indeed. As to the propriety of having her go through the night, if I were a beneficent dictator, I should advise that any patient with acute abdominal pain and vomiting in which there is any doubt whether something more than a functional disturbance exists should go to a hospital. But perhaps that is too much to expect, and certainly the course of this case justified her being kept where she was. We surgeons know that the possibilities of acute abdominal pain and vomiting are so great that we should like to have had her under hospital observation where interferences could have been carried out if necessary. The night is quite long for a patient with acute abdominal pain.

"She had one small, liquid, pinkish bowel movement." That is extremely interesting and important; undoubtedly the color was due to blood. Something caused bleeding into the gastrointestinal tract. The most probable thing would be an ulcer. We do not know whether she had previously had occult blood in the stools, but here definite gross blood appeared, which suggests ulceration. But bear in mind that it also suggests interference with the circulation in the intestine somewhere, or strangulation, or acute passive congestion, with a little leakage into the intestinal loop. Indeed, that is extremely important.

It is perfectly evident that the doctor became convinced that the disturbance in the upper abdomen should be under surgical observation.

It is interesting that the patient had had anemia for years and had had liver therapy, but it is obvious that she did not have pernicious anemia. It is just possible that she had had for years some lesion in the bowel that had been leaking a little bit, not causing enough bleeding to be observed but enough to cause anemia; possibly there was a connection between that and the present condition.

This patient had had a laparotomy and uterine suspension thirty-three years before entry. I should like to call to your attention that whenever the surgeon sees an abdominal scar he attributes a great deal of importance to it. In the first place, whatever the condition was for which she was operated on, it may have recurred, and one particularly thinks of carcinoma. The second point is that there may be a condition in the abdominal wound itself that may be the cause of the present symptoms. Of course I refer to a weakened wound with interstitial hernia, which is evident to the examiner. The third point, and in this case much the most significant, is that the operation may have resulted in adhesions, which cause some sort of band that may be the cause of the symptoms. Thirty-three years is a long time for that. It would depend a great deal on the character of the operation. It says "uterine suspension," I suppose of the modified Watkins's type. It might have been an attachment of the fundus of the uterus to the abdominal wall, which makes a long pulled-out band that is just the kind of thing which loops of small intestine insinuate themselves around and give obstructive symptoms, but I am surprised that that could have occurred so long after the operation. It is possible that a hysterectomy was done at that time. Hysterectomy in the hands of the average surgeon in those days was not the same as it is now. There was no satisfactory effort made to repair the pelvic floor, and there was quite a long area, running from the pelvic brim across to the cervix, where adhesions could easily form and produce acute intestinal obstruction, owing to strangulation by a band due to the adhesions.

The physical examination does not mention whether there was vomiting after the initial nine spells, which would be interesting to know. There was little real spasm. Again we have no suggestion of peritonitis, and I call your attention to the fact that the typical syndrome of acute, complete, intestinal obstruction was absent, that is to say, pain, obstipation, distention and vomiting. There

was pain, and there had been vomiting, but there was no persistent obstipation or distention. So we do not have the inevitable syndrome of symptoms that necessitate a diagnosis of acute intestinal obstruction. Still there may be intestinal obstruction because all these elements of the syndrome may not be present.

"Peristalsis was almost entirely absent." The intestine got tired trying to pass things along, and that suggests a little bit the possibility of peritonitis. "Palpation anywhere in the abdomen gave rise to pain in the epigastrium." That would not be so in pancreatitis; as a rule, palpation would have to be more or less over the region of the pancreas if the pain were due to pancreatitis. This does suggest to me, however, that intestinal coils on palpation of the abdomen were pushed about from one part to the other, making traction on the root of the mesentery, which would cause pain in the epigastrium. There was no definite spasm or tenderness over the abdomen, and with acute pancreatitis there should be definite tenderness and spasm, although not the boardlike rigidity of the perforated viscus. No vaginal or rectal examination is mentioned. Of course they were done, and we may assume that they were negative.

"Examination of the blood showed a white-cell count of 17,300, with 86 per cent neutrophils." That is an indeterminate degree of leukocytosis. I call your attention to the fact that there may be a certain amount of hemoconcentration, which increases the white-cell count to a certain extent.

Then we come to the x-ray examination, and we might glance at the films. The small intestine normally contains little if any gas. It is almost always completely filled with fluid. In obstruction there is gas, and we must be able to differentiate small intestine and large intestine. There you see quite plainly the valvulae conniventes close together — so different from the haustra of the large intestine. The diameter of the bowel is distinctly increased, not markedly so. I am not sure whether this other loop is small intestine or large intestine. That may be normal large intestine. The one loop of distended small intestine almost certainly means obstruction. Another point is that there is no gas under the diaphragm, which, if this were taken in the standing position, would be evidence against perforation.

An operation was performed two hours after admission. I call your attention to the fact that probably we cannot, from this printed protocol, get a satisfactory idea of the patient's condition. From it I learn that she had a good night and came in without having had further vomiting, that the blood pressure fell a little and that the white-cell count was slightly elevated; the picture as given is not that of a very sick woman. The history, however, is extremely significant and it is perfectly clear that the experienced men who saw her made up their minds that it was an acute condition of a surgical nature. Let me remind you — I have it underlined here — that the most important factor was not the exact condition existing here, but whether it was a surgical emergency; in other words, whether there was a condition that might have been treated expectantly along medical lines, or whether she had to be explored. I am not going to enumerate all the causes of acute episodes like this in the abdomen with symptoms of at least partial obstruction, perhaps complete obstruction, but I am going to bring to your attention, of course, the question of Meckel's diverticulum. It must be remembered that, that being a congenital anomaly, it would be rather strange to have a Meckel's diverticulum become adherent late in life and form a band that became strangulated. If attached to the umbilicus it would have caused symptoms earlier. It is still a possibility. Another condition that I shall rule out from lack of antecedent history and from lack of x-ray confirmation is obstruction from a gallstone that had ulcerated into the intestine, although, let me say immediately, a large cholesterol gallstone can ulcerate through to the duodenum and a phlegmatic patient often gives no antecedent history, and the x-ray may not show it.

Then there is volvulus, but that does not appeal to me. There is intussusception. Intussusception, of course, is almost practically confined, except for a few cases that have been described, to the period of life before five years; most of them occur before one year of age. Intussusception of the terminal ileum into the cecum is the usual rule. But there is a form occurring in the adult that usually appears in the small intestine and is invariably due to the presence of a tumor, and in my experience usually a nonmalignant tumor, a lipoma or fibromyoma of the small intestine. The tumor gets caught in a peristaltic wave and gets drawn into the distal bowel; it is pulled along by peristalsis and forms a true intussusception that can relieve itself readily and may occur again and again. The first attack may be significant. If that occurred here it would have caused obstruction accompanied by acute passive congestion, with leakage of blood into the bowel. Moreover, we might link it up with the moderate degree of anemia for a considerable period, because such a tumor may have given rise to leakage from time to time, although I do not believe that that is important.

Pancreatitis, I am going to remind you, is always a possibility, but the lack of marked tenderness in the epigastrium and pain in the back, the very sudden onset, which is not characteristic of pancreatitis, and the failure to get any antecedent history to suggest it practically rule out pancreatitis.

I see no cause for considering primary mesenteric thrombosis. There is nothing in the history to suggest arterial mesenteric embolism.

There is another point to stress, and I am perfectly certain that it was done here, and that is that one never fails, when confronted with a case like this, to examine with the greatest of care the region of inguinal and femoral hernias. In a woman, femoral hernia, especially in an adipose woman, may be so small as to be indistinguishable. The pain of hernia may not be referred to the site of the hernia but to the epigastrium because of the pull on the mesentery of the bowel which is attached there. I know of two cases in which, because of the combination of an ultramodest patient and a diffident physician, the site of femoral hernia was not examined and therefore operation was delayed, with resulting exitus.

So far as operation is concerned, the anesthesia was probably spinal, although some people think that the inhibition of the sympathetic nerves leading to increased peristalsis produced by spinal anesthesia might be harmful in intestinal obstruction. Local anesthesia and gas would be fairly satisfactory. If a general anesthetic were used, especially ether, we would surely pass a stomach tube first and keep it in place during anesthesia. There is nothing more fatal than the vomiting that occurs under ether anesthesia in cases of intestinal obstruction. I presume a paramedian incision was made, starting at the umbilicus.

Dr. Benjamin Castleman: Would you like to state your first choice?

Dr. Cheever: Intussusception due to tumor, probably benign, of the jejunum.

Dr. Arthur W. Allen: I should like to compliment Dr. Cheever on his masterly discussion of this patient. He has covered the situation with great thoroughness.

This patient happened to be the widow of a physician who was a colleague of mine in World War I. I have known her a good many years. I had never seen her professionally, but I had known that she had a hard time keeping a normal weight and that she had a good deal of gastrointestinal difficulty requiring special diet — iron, liver and so forth.

Dr. John T. Quinby is the man who saw her first and realized that she was an ill woman. He talked to me about her on the telephone about seven o'clock in the evening, and I suggested that it would be all right to give her a little relief with 1/6 gr. of morphine and that if she did not get better from the "ptomaine poisoning" which she was sure she had, I would come in to see her. I did see her about nine-thirty that night and could not, for the life of me, bring myself to think that she represented an acute abdominal emergency. The lack of high-pitched peristalsis, the fact that the vomitus at that time was nothing but undigested food, with no evidence of intestinal contents, the repeated stools, the reference of her pain to the epigastrium, with actually more tenderness in the epigastrium than elsewhere, made me believe that my second choice, after acute gastrointestinal upset, was pancreatitis.

In defense of Dr. Quinby I might say that we tried to get her into the hospital, but there were no beds; so the best we could do was to get a nurse and Dr. Quinby stayed with the patient through the night, keeping his eye on her. I thought that was as adequate as having her in the hospital, where we should undoubtedly have kept her under observation much the same way.

The next morning, at six o'clock, it was obvious to us that she was still ill, and finally the Admitting Office decided we could have a bed in the Emergency Ward. We got her in and immediately had this x-ray film made, which, of course, clinched the diagnosis. But before this film was made and before Dr. Quinby told me there was blood in the stool that she passed during the night, I thought that this woman had a medical disease, not a surgical belly; that is how close we came to missing it.

Clinical Diagnosis

Intestinal obstruction, small bowel.

Dr. Cheever's Diagnoses

Intestinal obstruction.
Intussusception due to tumor, probably benign, of jejunum.

Anatomical Diagnoses

Intestinal obstruction.
Infarction of small intestine due to adhesive band.

Pathological Discussion

Dr. Allen: At operation we found intestinal obstruction due to a band that was running from the region of the right upper quadrant across the terminal ileum, very close to the cecum, but far enough away to allow the entire mesentery of the small bowel to rotate around it. There was an enormous amount of dead terminal ileum due to thrombosis of the vessels that had become occluded mechanically by the torsion. The band ran down to the region of the old suspension — a very small band, not more than 2 mm. in diameter.

I was confronted with the problem of how much small intestine she could spare. She had had a hard time getting on with what she had been born with. So I started at the terminal ileum and removed the bowel up to a point where I thought there was some chance for the rest of it to come back, taking out 71 cm., which is an appreciable length. We then observed the other 100 cm. or so of small bowel that was involved, which made a fairly satisfactory return. I had to gamble that complete circulation would be restored to the latter segment, since I knew that, had I taken it out, she would certainly

have suffered from a deficiency state. Anastomosis between the ileum and the cecum was done, and she made a pleasant and uneventful convalescence.

DR. CHEEVER: There are two things I should like to say. The first is to emphasize the impossibility, in a case of intestinal obstruction, of deciding, with any certainty, whether or not strangulation exists. I think Dr. Allen will bear me out in this — until the matter has reached the final stage there are certain things one cannot be sure of. The other thing, which I say with the utmost sincerity, is that this patient was fortunate that she fell into the hands of someone who knew what he was doing. When I learned that it was a good friend of mine, I was much pleased, but to spare his blushes I should not say so.

CASE 30262

PRESENTATION OF CASE

First admission. A sixty-three-year-old watchman entered the hospital because of gnawing abdominal pain.

The patient had been in apparent good health until nine months before entry, when he noticed frequent attacks of heartburn, which came on a few hours after eating and were relieved by soda and food. Three months before entry he was seen in the Out Patient Department, where a gastrointestinal series showed a small crater in the pylorus. He was placed on a six-meal bland diet and tincture of belladonna. In the course of the next two months he experienced considerable relief, and x-ray films showed definite evidence of healing. A gastric analysis showed no free acid in the fasting specimen and only 38 units after histamine injection. During the month prior to admission the patient had recurrence of the heartburn and lack of appetite.

Physical examination on admission showed a well-developed, well-nourished, but pale man. The heart, lungs and abdomen were normal.

The blood pressure was 120 systolic, 75 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,600,000, with 12 gm. of hemoglobin. The white-cell count was 8500, with 67 per cent neutrophils. The urine was normal. A blood Hinton test was negative. The stools were guaiac negative. A gastrointestinal series (three and a half months after the first studies) showed a large crater above the angle of the stomach, slightly toward the anterior wall. Below this point there appeared to be one or more smaller craters.

The patient was given a gastric diet and atropine. After two weeks on this regime repeat x-ray studies showed the large ulcer to be approximately the same size as it was in the previous examination. Accordingly, a subtotal gastrectomy and posterior antiperistaltic Hofmeister anastomosis were performed. The pathological examination showed peptic ulcers without any evidence of malignant disease. Postoperatively the patient did well, and he was discharged home on the thirty-seventh hospital day.

Final admission (one month later). Following discharge the patient remained well until six days before readmission, when he had two chills without fever, felt ill and went to bed. Two days later he vomited whitish, questionably bile-stained material. About that time he noted the onset of jaundice. Subsequently, the stools became clay colored, and the urine dark. At no time did he experience pain or have fever. He had had no previous jaundice.

Physical examination showed a moderate degree of jaundice. There were tenderness and voluntary spasm in the right upper quadrant. On deep inspiration the liver edge was palpable 5 cm. below the costal margin in the anterior axillary line. Examination was otherwise negative.

The blood pressure was 95 systolic, 60 diastolic. The temperature was 98.6°F., the pulse 85, and the respirations 20.

Examination of the blood showed a white-cell count of 5200. The hemoglobin was 82 per cent. The stools were clay-colored, with brown streaking and a ++ guaiac test. The urine was normal. The blood nonprotein nitrogen was 35 mg., and the protein 5.2 gm. per 100 cc. The blood chloride was 98 milliequiv. per liter. The van den Bergh was 10.3 mg. direct, and 14.6 mg. indirect. A film taken after one swallow of barium showed the barium to pass readily through the stoma into the nondilated efferent loop. The spleen was slightly enlarged. A film of the abdomen was normal.

The patient was given intravenous fluids. The jaundice increased. In the course of the next six days, the direct van den Bergh rose to 18.6 mg. per 100 cc., and the indirect to 24.4 mg. A bromsulfalein test revealed 100 per cent retention.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: I have no idea what a "posterior antiperistaltic Hofmeister anastomosis" is. It might be important in this case. Presumably this patient had transfusions at that time, but I want to know definitely whether he did. That is a fair question, I believe.

DR. BENJAMIN CASTLEMAN: He was given two transfusions.

DR. RICHARDSON: That is enough.

I take it that the two chills he had were real, otherwise they would not be put in the abstract.

I should also like to know whether he had ever had any fever. I should prefer that he had fever during the second admission.

DR. CASTLEMAN: Here is the chart.

DR. RICHARDSON: He had a temperature of 101°F. by rectum for one day.

"The van den Bergh was 10.3 mg. direct, and 14.6 mg. indirect." As I have said many times before, the latter is misleading. The 14.6 mg. is the total bilirubin. One has to subtract 10.3 from 14.6 to get what we ordinarily consider the indirect. In other words, the van den Bergh test showed that two thirds the bilirubin was demonstrated by the direct method, which of course is suggestive evidence of obstructive jaundice. The bromsulfalein test showed 100 per cent retention, which anyone would have predicted in a patient with this degree of jaundice. There is no point in doing this determination in the presence of severe jaundice.

I should like to make a comment or two about the laboratory findings before I go on to differential diagnosis. The first is about the blood. In this case a blood smear would have been helpful. If it had shown some abnormal lymphocytes, suggesting mononucleosis, I do not believe that this would have been detected on the surgical service and probably not always on the medical service. This finding would be of some differential importance, suggesting infectious hepatitis. Another thing I want to comment on is the total protein of 5.2 gm. If that was an accurate determination it is definitely low.

In regard to differential diagnosis, I am going to take up only three possibilities: silent stone in the common duct; adhesions or distortion due to ulcer or possibly postoperative inflammation resulting in obstruction to the common duct; and acute infectious hepatitis.

I do not believe this patient had stones. My chief reason for this statement is that the combination of gallstones and ulcer in the same patient is almost unheard of. If anyone has heard of that combination I should be glad to have him speak up. It is a striking thing that the ulcer habitus and the gallstone habitus are quite different, and I do not believe that I have ever seen the two diseases in the same patient. There are other features about the case that are against stone. He had had no previous attacks of pain, but of course one can never rule out stone on that basis.

Now what about the question of jaundice due to ulcer? One can have jaundice due to ulcer in the region of the ampulla, or one might have a considerable inflammatory reaction around an ulcer that was near the ampulla, but one would not get it from ulcer in or above the pylorus. There is no mention or suggestion of ulcer below the pylorus, so I think that that can be ruled out.

That brings up the question of an inflammatory postoperative reaction. Just why there should have been a considerable amount of inflammatory reaction in the region of the common duct, I am not sure; but it would seem possible as a result of the rather complicated gastric surgery that went on. The sudden onset with chills is very much opposed to that diagnosis, however. I should expect a gradual onset with jaundice and nothing else — a rather slow progression of severe and intense jaundice after a period of a good many weeks. This was rather sudden in onset, with chills and possibly fever and then severe jaundice, an apparent rapid increase in the size of the liver and possibly splenomegaly by x-ray examination.

I therefore think that the evidence is in favor of infectious hepatitis. If so, what was the cause of it? One would have at least to bring up the possibility that it was caused by the transfusion that was received at the previous operation. My diagnosis is infectious hepatitis possibly secondary to transfusion.

I want to say one more thing, which is certainly true whether I am right or wrong about the diagnosis. There was no particular hurry about operating on this patient. It seems to me that he was operated on too quickly. He should have been kept in bed and watched for a while. Now that we know that we can protect against prothrombin lack, there is not too great a risk. It is less of a risk to be sure that one does not operate on a patient with a sick liver due to hepatitis.

DR. CASTLEMAN: How do you tie up the transfusion with the infectious hepatitis?

DR. RICHARDSON: I was thinking of the modern theory that transfusions from donors who have had jaundice due to hepatitis within a year may be able to transmit the disease to the recipient. There have been some deaths. I believe that it has occurred in all situations involving the injection of human serum. The thought is that the disease is due to a virus.

DR. EARLE M. CHAPMAN: I want to comment on Dr. Richardson's second possibility — a postoperative inflammation about the common duct or head of the pancreas — to explain this man's jaundice. When visiting on the West Medical Service recently I saw four patients with the same pattern of jaundice following surgery for duodenal ulcer, and yet the surgeons insisted that there was no relation between the two. Two of these patients recovered gradually. The chief finding in both was marked tenderness in the epigastrium, suggesting an inflammatory reaction.

CLINICAL DIAGNOSIS

Obstructive jaundice.

DR. RICHARDSON'S DIAGNOSIS

Infectious hepatitis, possibly due to transfusion.

ANATOMICAL DIAGNOSES

Intrahepatic cholangitic biliary cirrhosis.
Acute hemorrhagic pancreatitis, with fat necrosis.
Icterus.
Bile nephrosis.

Operation: subtotal gastrectomy with posterior gastrojejunostomy.
Bronchopneumonia, diffuse.

Pathological Discussion

Dr. Castleman: At operation the surgeon found the peritoneal cavity remarkably free of adhesions. There was a small amount of bile-stained fluid. There was no dilatation of the duodenum or of the afferent loop. The pancreas was normal in size and consistence. By pressure on the gall bladder he was able to empty it into the duodenum and to aspirate thin greenish bile from an inlying nasal tube. He palpated the entire common duct and found no evidence of stone, tumor or other obstruction. The liver was yellowish-green, tense and firm. Since no obstruction was found, nothing further was done.

Following operation the patient continued to do poorly, became drowsy and disoriented and died on the eleventh postoperative day.

The autopsy showed a normal-sized liver, which was definitely green and slightly firmer than normal. The gall bladder appeared normal. The common duct was perhaps slightly thickened, but normal in size, patent and free from stones. In the region of the head of the pancreas we found a mass measuring 8 cm. in diameter; this was a bit fluctuant and, when cut into, appeared to be an acute hemorrhagic affair. Scattered all over the surface were areas of fat necrosis. There is no question that this was acute pancreatitis. This mass could not have been present at operation ten days before because it would have been easily seen. The manipulation of the gall bladder at operation possibly forced some bile into the pancreatic duct, thus producing the pancreatitis.

Microscopically the liver presented a very unusual process. There was widespread parenchymal

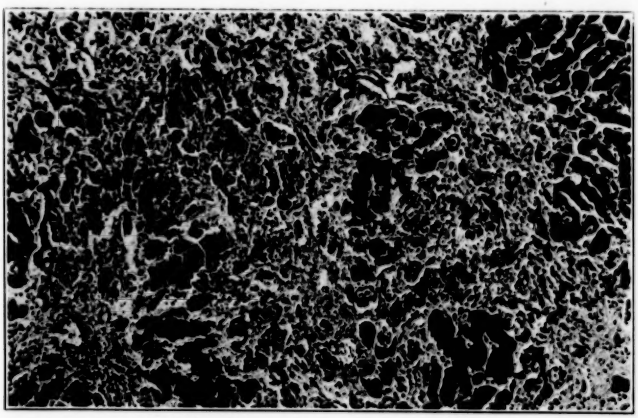

Figure 1. *Photomicrograph of Liver, Showing Widespread Liver-Cell Damage.*

destruction involving from half to two thirds of each liver lobule, which was replaced by granulation tissue infiltrated with lymphocytes and large numbers of polymorphonuclear cells (Fig. 1). There was bile stasis in the tiny bile canaliculi, which were tremendously distended and filled with so-called "bile thrombi" (Fig. 2). This is somewhat similar to the appearance that one sees with an extrahepatic obstructive biliary type of cirrhosis. In this case we were unable to find any extrahepatic biliary obstruction. Karsner,* in a recent review of the literature on hepatic cirrhosis, has used the term "intrahepatic cholangitic biliary cirrhosis," a diagnosis that I believe can be applied to this case. It is an intrahepatic obstructive and infectious process. The lesion, if we go back to when the patient had his first chill, was about twenty-three or twenty-four days old, and microscopically the picture is consistent with that age. One might ask, What is the relation between the liver disease and the acute pancreatitis? Of course, if the acute pancreatitis had occurred first we might assume that it had ob-

*Karsner, H. T. Morphology and pathogenesis of hepatic cirrhosis. *Am. J. Clin. Path.* 13:569-606, 1943.

structed the papilla and that the infection had spread up the lymphatics into the liver. The absence of dilatation of the common duct, both at operation and at autopsy, as well as the fact that it seems unlikely that the pancreatitis could have been overlooked at operation, rules out this possibility.

A PHYSICIAN: Was a blood culture taken?

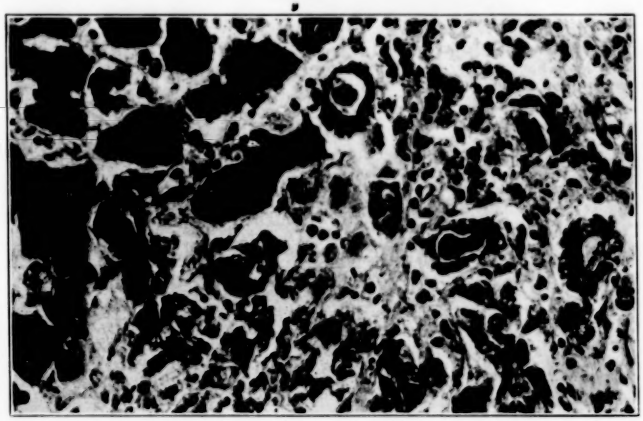

FIGURE 2. *Photomicrograph at a Higher Magnification, Showing Bile Thrombi and Inflammatory Reaction.*

DR. CASTLEMAN: The post-mortem culture showed a nonhemolytic streptococcus, which may have been a contaminant.

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RH TYPING SERUM

Rh typing serum is now available for all who need it. This should be welcome news to the obstetrician and to the physician or surgeon administering transfusions, who appreciate the importance of this new blood type and have been concerned because of the lack of diagnostic serum. For the doctor who is not aware of the dangers of Rh incompatibility, the letter regarding the practical aspects of this subject, published elsewhere in this issue of the *Journal*, should be informative.

Except for the important obstetric complications, the sequelae resulting from the repeated transfusions of Rh− recipients with Rh+ blood are obviously of greater concern to physicians in the armed forces than to those in civilian practice. For the former often uses multiple transfusions in the treatment of hemorrhage, shock, blast or burn injury, or chronic infection, and the one man in seven who is Rh− deserves the protection that is offered by this special typing of blood.

The early and, until recently, the chief handicap to differentiation of Rh+ and Rh− red cells was the scarcity of potent, rapidly active serum. The supply of such material was dependent on the identification of high-titered anti-Rh agglutinins in the blood of the rare woman who built up these antibodies during and maintained them after the birth of one or more infants with erythroblastosis fetalis. Statistically, such an event occurs about once in more than 5000 deliveries. Even if such women were willing and able to donate a pint of blood frequently, the supply of anti-Rh serum from this source alone would fall far short of meeting the usual demand of civilian hospitals and the expanded needs of military establishments. It was therefore necessary to develop a method whereby larger amounts of Rh typing serum are available for immediate use. This project is explained in the letter referred to above, and co-operation of all physicians will ensure its success, thus benefiting chiefly the members of the armed forces at the moment, and everyone after the present emergency passes.

After the war it seems likely that Rh typing will assume even greater significance than it does at present. Certainly, whole blood and resuspended red cells will be readily available and will probably be used freely. The Rh− men returning to civilian life who received one or more transfusions of whole blood during the war may have developed an appreciable titer of Rh agglutinins if Rh+ blood was used, and on being again transfused, severe hemolytic reactions may occur following the injection of Rh+ red cells. Furthermore, the current civilian needs for Rh typing will not diminish. For these reasons, proper Rh typing serum will be required in abundance. The present project offers promise of meeting the need.

THE "OFFENSIVE" ODOR OF GARLIC AND ONIONS

A FEW years ago the American medical profession was greatly amused, if not much enlightened, by two articles concerning garlic breath that appeared in the *Journal of the American Medical Association*.[1, 2] A recent issue of the *American Review of Soviet Medicine*[3] calls attention to a series of scientific investigations on the possible beneficial effects of the vapors of these alliaceous plants when used as bactericides or as phytoncides (plant bactericides).

The therapeutic possibilities of garlic have, in the past, been studied and utilized to a varying degree even in this country and in Great Britain. It has been used in the treatment of infectious diseases such as pneumonia,[4] as an antihelminthic[5] and in the treatment of hypertension.[6] Observations have been made on the bactericidal effect of garlic and onions in vitro against many bacteria,[7] including *Mycobacterium leprae*.[8] A systematic study was also reported on the physiologic effects of garlic and of derived substances.[9] Some of these were found to be highly toxic, whereas others, which are noxious for bacteria or other parasites, are apparently nontoxic and thus have therapeutic possibilities.

The Soviet investigators summarized the results of many experiments concerning the phytoncidal activity of alliaceous plants. They found that extremely small amounts of a paste of freshly macerated onion, garlic or similar plants emit enough phytoncide to kill all exposed unicellular organisms within one to five minutes. They found no protozoa that were resistant to the phytoncide of garlic or onions. They also demonstrated that free-living infusoria and certain flagellates are affected. In certain paramecia, they noted first an apparent stimulation of motility, followed by specific morphologic changes that continued after all motility had ceased. Other investigations indicated that large concentrations of these vapors introduced into animals by inhalation caused a rather pronounced stimulation of the wandering cells of the connective tissue but no parenchymatous changes in the organs.

The Russian workers went on farther, applying these plant phytoncides in the treatment of infected wounds. Gratifying results were obtained in many cases of delayed healing, particularly amputated stumps in which there was considerable purulent inflammation of the wound. Regeneration of tissues proceeded rapidly in spite of the frequent dressings required by the treatment. All the clinical results, however, were not favorable. In some cases, epithelization stopped suddenly after a few treatments, and in others, there was an increase in granulation tissue and a lack of epithelization in other parts of the wound.

These findings may serve to intensify the interest in finding new remedial agents derived from living plants, including micro-organisms. The practical results are well exemplified in the great advances that followed the discovery of gramicidin and penicillin. The finding of new and effective substances leads, in turn, to identification of the active principles with a view to defining the chemical structure of the agents responsible for the various beneficial activities, as well as those associated with toxic properties. Eventually this should lead to synthesis of similar or related chemical compounds having the optimum therapeutic activity and the least injurious effects.

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CORRESPONDENCE

RH TYPING SERUM

To the Editor: In 1940, Landsteiner and Wiener discovered a new antigenic substance in the blood — the Rh factor — present in 87 per cent of the white population and absent in 13 per cent. At first it was thought to have no practical or clinical importance. It was soon demonstrated by Levine and by Wiener, however, that Rh– persons (those lacking this Rh agglutinogen) might, under certain circumstances, develop immune antibodies against the Rh factor and suffer serious consequences from the action of such anti-Rh agglutinins.

Abundant evidence has been collected by now to show that anti-Rh agglutinins may be developed in Rh– males and females as the result of one or more transfusions with Rh+ blood, and in women by repeated pregnancies involving an Rh+ fetus (this blood type being inherited as a dominant characteristic from the father).

Recognized intragroup transfusion reactions due to Rh incompatibility have apparently been quite rare in civilian practice. This does not imply that Rh– persons who receive Rh+ blood fail to develop antibodies. On the contrary, data from the Blood Grouping Laboratory in Boston suggest that many such recipients develop weak agglutinins. Subsequent transfusion reactions are fairly mild unless numerous transfusions are given and agglutinins increase in strength. Probably the most important reason for the failure to note a higher percentage of hemolytic transfusion reactions of this type is that multiple transfusions are the exception in civilian practice, more than 95 per cent of the transfusions being single infusions of blood. In contrast to this, in the treatment of members of the armed forces, multiple transfusions are exceedingly common, and therefore transfusion reactions in the 13 per cent of the population who are Rh– are quite likely to become more frequent and severe, thus interfering with benefit from the procedure, with speed of convalescence and even with eventual recovery. This has been borne out by the published statistics.

Because of the increasing availability of plasma and whole blood, and the attempt to diminish maternal mortality due to hemorrhage and puerperal sepsis, transfusions are now given to patients on obstetric services much oftener than in days past. In contrast to the experience with medical or surgical cases, a first transfusion of Rh+ blood to an Rh– mother who has been sensitized by pregnancy with an Rh+ fetus may be followed by a fatal reaction. Also an Rh– woman of child-bearing age, given Rh+ blood, will be sensitized and will develop anti-Rh agglutinins; if she then has a pregnancy involving an Rh+ fetus the child will develop erythroblastosis, often of the severest type.

To sum up the accumulated facts, it may be stated that Rh incompatibility is of practical importance under the following conditions:

(1) Rh– recipients, men and nongravid women, who receive repeated transfusions of Rh+ blood may have intragroup hemolytic transfusion reactions. Such reactions do not occur following the first transfusion; but after a suitable interval for the development of antibodies, further transfusions produce signs of increasing hemolytic reaction with jaundice, anemia and, finally, anuria.

(2) Rh infants born to mothers who have anti-Rh agglutinins may show varying degrees of hemolytic anemia of the newborn, or erythroblastosis fetalis. The severer forms are characterized by late fetal death with congenital hydrops and icterus gravis. In this situation, Rh typing of the mother, father, and child is of diagnostic value, and demonstration of anti-Rh agglutinins in the mother may fix an otherwise questionable diagnosis.

(3) Serious and even fatal hemolytic transfusion reactions may result from the *first transfusion* in Rh– women who have been sensitized and have developed anti-Rh agglutinins through pregnancies.

(4) The use of Rh+ blood for transfusion of Rh– women, even for the first time, may initiate the formation of anti-Rh agglutinins and produce erythroblastosis of a severe or fatal form in their Rh+ offspring.

For the above reasons, it has become apparent that Rh typing should be carried out in the following persons:

(1) Recipients of whole blood or of resuspended red cells, especially if multiple transfusions are contemplated, in order to avoid giving an Rh– patient Rh+ blood. It is most important to type recipients of multiple transfusions or persons having a history of previous transfusions. Donors and stored blood should also be typed for the Rh agglutinogen so that suitable blood is available for Rh– patients.

(2) Any woman whose history suggests the possibility of erythroblastosis — either by one or more stillbirths or infants born with hydrops, jaundice or anemia — before even a first transfusion is given, since a fatal reaction may occur.

(3) Women of child-bearing age before transfusion, since Rh– women given Rh+ blood may be so sensitized that future pregnancies will result in dead or damaged infants.

(4) Babies born with jaundice and anemia, in order that their recovery may be facilitated by transfusion with Rh– blood.

The military services require Rh typing serum even more urgently than do the civilian hospitals, since multiple transfusions are so much commoner in military institutions, and also because obstetric services are expanding in military establishments. It is necessary to have such serum not only for the typing of recipients, but also for the typing of prospective donors, either for Rh– patients or for a donors' list or for banked blood for emergency use. The most serious difficulty in this connection has been the relative paucity of available serum. The reasons for this are threefold:

(1) Experimental or animal serum is difficult to produce and gives agglutinations that are unreliable or difficult to read by the average technician.

(2) High-titered serum of human origin occurs chiefly in women recently delivered of erythroblastotic infants, and even here it is found in only 1 of 20 such women, or 1 in 4000 deliveries.

(3) Such high-titered serum may be extremely specific (70 per cent instead of 87 per cent positive reactions), and therefore may not be useful for general Rh testing. This makes the occurrence of high-titered useful serum about 1 in 6000 deliveries.

For these reasons, other means of increasing the supply of Rh typing material seemed required. It had been noted that low-titered anti-Rh serums were found ten times as frequently as high-titered serums. This material, however, was not safe for general laboratory use because the tests obtained were not clear cut and many negative results occurred with known Rh+ cells. Through the co-operation of the Department of Physical Chemistry of the Harvard Medical School such low-titered serum was concentrated into a globulin fraction yielding good typing results. This opened the possibility of utilizing the more abundant supply of serum containing low-titered Rh agglutinins and thereby possibly meeting the need for Rh typing material.

Accordingly, a project was started under contract from the Committee on Medical Research of the Office of Scientific Research and Development for the collection and preparation of Rh typing serum. During the past six months, meetings have been arranged with obstetricians, pediatricians and clinical pathologists in all the large medical centers, and the facts regarding the need for Rh typing serum have been presented. It has been suggested that they send a few cubic centimeters of blood from any patient known to them to have had a baby with erythroblastosis or possible erythroblastosis (including late fetal death of undiagnosed cause) delivered within the last two years. If the serum, by in vitro tests, shows a useful amount of anti-Rh agglutinin, the physician is notified and requested to obtain from the patient 100 to 500 cubic centimeters of blood which is to be shipped promptly. Such material is pooled for concentration of the anti-Rh agglutinin, and a useful typing globulin is produced. Seventy per cent of the resulting serum is set aside for use by the military services, and 30 per cent is credited to the hospital or physician contributing in this enterprise. Such a credit can be drawn on immediately in the form of standard Rh typing serum, so that any hospital or laboratory may have its own material without delay. Special pre-addressed containers and test tubes are being sent to all physicians and hospitals co-operating in this project so that shipment of specimens may be expedited. Also collecting bottles and pre-addressed containers for sending blood serum via air express, collect, are obtainable on request.

Only through such a co-operative enterprise for obtaining large amounts of Rh typing serum does it seem possible to meet the urgent and increasing needs of the military forces, as more whole blood is being used; also by this means it is hoped to supply the immediate and future demands of obstetric and general hospitals.

All requests for information and for material should be addressed to the Blood Grouping Laboratory, 300 Longwood Avenue, Boston 15, Massachusetts.

Louis K. Diamond, M.D.
300 Longwood Avenue
Boston 15

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